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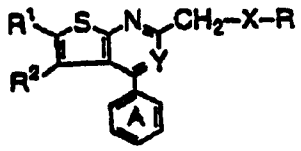
(54) Title: THIENOPYRIDINE OR THIENOPYRIMIDINE DERIVATIVES AND THEIR USE



(I)

(57) Abstract

This invention provides anti-inflammatory agents, particularly agents for treating arthritis, and bone resorption inhibiting agents containing a thienopyridine or thienopyrimidine derivative of formula (I) or a salt thereof. This invention also provides a novel thienopyridine or thienopyrimidine derivative having anti-inflammatory activity and bone resorption inhibiting activity.

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DESCRIPTION

THIENOPYRIDINE OR THIENOPYRIMIDINE DERIVATIVES AND THEIR USE

TECHNICAL FIELD

This invention relates to a novel thienopyridine or a novel thienopyrimidine derivative or a salt thereof, which is useful as an anti-inflammatory agent, especially a therapeutic agent of arthritis, and which is useful as a prophylactic or therapeutic agent against osteoporosis.

BACKGROUND ART

Arthritis is an inflammatory disease of the joint, and, as principal diseases, are mentioned rheumatoid arthritis and related diseases with joint inflammation.

Among them, especially rheumatoid arthritis, also called chronic arthrorheumatism, is a chronic multiple arthritis characterized by inflammatory changes in the synovial membrane of the articular internal capsule layer. Arthritic diseases like rheumatoid arthritis are progressive and cause joint disorders such as deformation and ankylosis, often resulting in severe physical disorder due to lack of effective treatment and subsequent deterioration.

Traditionally, these forms of arthritis have been chemotherapeutically treated with various agents, including steroids such as cortisone and other adrenocortical hormones; non-steroidal anti-inflammatory agents such as aspirin, piroxicam and indomethacin; gold agents such as aurothiomalate; anti-rheumatic agents such as chloroquine preparations and D-penicillamine; antipodagric agents such as colchicine; and immnunosuppressors such as cyclophosphamide, azathiopurine, methotrexate and

levamisole.

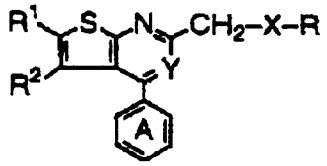
However, these drugs have drawbacks such as severe adverse reactions, adverse reactions hampering the drug's long-term use, lack of sufficient efficacy and a failure to be effective against already-occurring arthritis.

Accordingly, development of a drug performing excellent prophylactic/therapeutic action on arthritis with low toxicity has still been desired from the clinical viewpoint.

Traditionally, various compounds have been synthesized as thieno[2,3-b]pyridine derivatives, which are disclosed in, for example, Bull. Chem. Soc. Jpn., 61, 4431 (1988), Chem. Pharm. Bull., 36, 4389 (1988), Phosphorus, Sulfur, and Silicon, 73, 127 (1992), Chem. Pharm. Bull., 40, 1376 (1992), and Khim. Geterotsikl. Soedin., 1, 124 (1987). In those compounds, the substituent at 6-position of the thieno[2,3-b]pyridine skeleton is restricted to methyl group. And, no description of anti-inflammatory activities is given on these known thienopyridine derivatives. In Journal fuer praktische Chemie, 317, 705 (1975), the synthesis of thieno[2,3-d]pyrimidine derivatives having methyl group or acetoxymethyl group at 2-position is described. And, in Japanese Patent Unexamined Publication (Kokai tokkyo koho) No. 43796/1976 [Chemical Abstracts, 85, 94398r (1976)], there are disclosed thieno[2,3-d]pyrimidine derivatives having carboxylethyl group at 2-position. However, there has been no report of any derivative having a carbon chain substituted with heterocyclic group or amino group at 2-position of these thieno[2,3-d]pyrimidine skeleton. And, no description of inhibitory activity of bone resorption is given on these known thienopyridine or thienopyrimidine derivatives.

DISCLOSURE OF INVENTION

The present inventors found that the novel thienopyridine or thienopyrimidine derivatives represented by the formula (I):

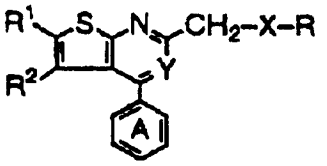


(I)

have anti-arthritic activity and are useful as a joint destruction suppressor and have inhibitory activity of bone resorption and are useful as a prophylactic or therapeutic agent against osteoporosis, and accomplished the present invention.

More specifically, the present invention relates to:

(1) A compound represented by the formula (I):



(I)

wherein R^1 and R^2 independently stand for a hydrogen atom, a halogen atom or an optionally substituted alkyl group, or R^1 and R^2 may be combined to form a 5- to 7-membered ring; Y stands for a nitrogen atom or C-G, G stands for an optionally esterified carboxyl group; X stands for an oxygen atom, an optionally oxidized sulfur atom or $-(CH_2)_q-$ (q denotes an integer of 0 to 5); R stands for an optionally substituted heterocyclic group or an optionally substituted amino group; and ring A may optionally be substituted, or a salt thereof.

(2) The compound of above item (1), wherein the optionally substituted alkyl group for R^1 or R^2 is independently a straight-chain or branched-chain C_{1-6} alkyl group; the optionally substituted 5- to 7-

membered ring for R^1 and R^2 is (i) a C_{5-7} alicyclic hydrocarbon group, or (ii) a heterocyclic group containing one to 4 oxygen atom, one to 4 sulfur atom which may be oxidized, or one nitrogen atom which may be substituted by optionally substituted C_{1-10} alkyl; the optionally substituted heterocyclic group for R is (i) a 5- to 7-membered heterocyclic group containing one sulfur atom, one nitrogen atom or one oxygen atom, (ii) a 5- to 6-membered heterocyclic group containing 2 to 4 nitrogen atoms, (iii) a 5- to 6-membered heterocyclic group containing 1 to 2 nitrogen atoms and one sulfur atom or one oxygen atom, or (iv) a group formed by condensation of each of the above three groups with a 6-membered group containing two or less nitrogen atom, a benzene ring or a 5-membered ring containing one sulfur atom; or the optionally substituted amino group for R is represented by $-N(R^3)(R^4)$, in which R^3 and R^4 independently stand for a hydrogen atom, an optionally substituted hydrocarbon residue or an optionally substituted heterocyclic group, or R^3 and R^4 are combined to form a nitrogen containing cyclic group; and the substituent of ring A is substituted by a halogen atom, a nitro group, an optionally substituted alkyl group, an optionally substituted hydroxyl group, an optionally substituted thiol group, an optionally substituted amino group, an acyl group, an optionally esterified carboxyl group or an optionally substituted aromatic cyclic group.

(3) The compound of the above item (2), wherein an optionally substituted 5- to 7- membered ring for R^1 and R^2 is represented by the formula of $-R^1-R^2-$, which is $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-CH_2-N(R^5)-CH_2-CH_2-$ (R^5 is C_{1-4} alkyl which may be substituted by phenyl), $-CH_2-S-CH_2-CH_2-$, $-CH_2-SO-CH_2-CH_2-$, $-CH_2-SO_2-CH_2-CH_2-$, or $-CH_2-O-CH_2-CH_2-$.

(4) The compound of the above item (2), wherein

the optionally substituted hydrocarbon residue for R^3 or R^4 is independently

a C_{1-8} saturated aliphatic hydrocarbon residue,

a C_{2-8} unsaturated aliphatic hydrocarbon residue,

a C_{3-7} saturated alicyclic hydrocarbon residue,

a C_{5-7} unsaturated alicyclic hydrocarbon residue,

a C_{4-9} alicyclic-aliphatic hydrocarbon residue,

a C_{7-9} phenyl alkyl, a C_{11-13} naphtyl alkyl, a phenyl or a naphthyl;

the optionally substituted heterocyclic group for R^3 or R^4 is independently (i) a 5- to 7-membered heterocyclic group containing one sulfur atom, one nitrogen atom or one oxygen atom, (ii) a 5- to 6-membered heterocyclic groups containing 2 to 4 nitrogen atoms, or (iii) a 5- to 6-membered heterocyclic group containing 1 to 2 nitrogn atoms and one sulfur atom or one oxygen atom, which may be condensed with a 6-membered ring containing one or two nitrogen atoms, benzene ring or a 5-membered ring containing one sulfur atom; and

nitrogen containing cyclic group comprising R^3 and R^4 is 5- to 7-membered one.

(5) The optionally substituted heterocyclic group for R^3 or R^4 is independently an aromatic monocyclic-heterocyclic group, an aromatic condensed heterocyclic group, or a non-aromatic heterocyclic group.

(6) The compound of the above item (5), wherein (i) the aromatic monocyclic-heterocyclic group for R^3 or R^4 is independently furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl or triazinyl;

(ii) the aromatic condensed heterocyclic group for R^3

or R^4 is independently benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl or 1,2,4-triazolo[4,3-b]pyridazinyl;
or (iii) the non-aromatic heterocyclic groups for R^3 or R^4 is independently oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl or piperazinyl.

(7) The compound of the above item (4), wherein the 5- to 7- membered nitrogen containing cyclic group for R^3 and R^4 is independently 1-pyrrolidinyl, 1-imidazolidinyl, 1-pyrazolidinyl, 1-piperidinyl, 1-piperazinyl, 4-morpholinyl, 4-thiomorpholinyl, homopiperazin-1-yl, pyrazol-1-yl, imidazol-1-yl, 1,2,4-triazol-1-yl, 1,3,4-triazol-1-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, tetrazol-1-yl, benzimidazol-1-yl, indol-1-yl or indazol-1-yl.

(8) The compound of the above item (2), wherein the optionally substituted hydrocarbon residue for R^3 or R^4 is independently a straight- or a branched-chain C_{1-6} alkyl.

(9) The compound of the above item (2), wherein as a substituent for ring A, (i) the halogen atom is

fluorine, chlorine, bromine or iodine; (ii) the optionally substituted alkyl group is C_{1-10} straight-chain alkyl, C_{3-10} branched-chain alkyl or C_{3-10} cyclic alkyl; (iii) the optionally substituted hydroxyl group is hydroxyl, C_{1-10} alkoxy, C_{2-10} alkenyloxy, C_{2-10} alkynyloxy, phenyl-C_{1-4} alkyloxy, C_{2-4} alkanoyloxy, phenoxy or 4-chlorophenoxy; (iv) the optionally substituted thiol group is thiol group, C_{1-10} alkylthio, C_{2-10} alkenylthio, C_{2-10} alkynylthio, phenyl-C_{1-4} alkylthio, C_{2-4} alkanoylthio or phenylthio; (v) the optionally substituted amino group is amino group which may be substituted by C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aromatic group, hetero cyclic group or C_{1-10} acyl group; (vi) the acyl group is formyl or ones formed by bondage of C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or an aromatic group with carbonyl group; (vii) the optionally esterified carboxyl group is a group represented by the formula $-COOR^6$, wherein R^6 is a hydrogen atom, C_{1-6} alkyl group, aryl-C_{1-6} aralkyl group or aryl group; (viii) the optionally substituted aromatic cyclic group is C_{6-14} aromatic hydrocarbon group or aromatic heterocyclic group.

(10) The compound of the above item (1), wherein G is a group represented by the formula $-COOR^6$, whose R^6 is a hydrogen atom, C_{1-6} alkyl, aryl-C_{1-6}alkyl or aryl.

(11) The compound of the above item (1), wherein X is $-(CH_2)_q-$ (q is an integer of 0 to 3).

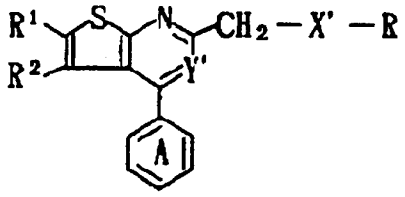
(12) The compound of the above item (11), wherein q is O.

(13) The compound of the above item (1), wherein the ring A is substituted by at least one C_{1-6} alkoxy.

(14) The compound of the above item (1), which is Ethyl 6-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-2,3-dimethylthieno[2,3-b]pyridine-5-carboxylate,

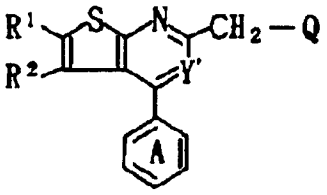
4-(3,4-Dimethoxyphenyl)-2-(N,N-diethylaminomethyl)-5,6-dimethyl-thieno[2,3-d]pyrimidine,
Ethyl 2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-5,6-dihydro-8H-thiopyrano[4',3'-:4,5]thieno[2,3-b]pyridine-3-carboxylate,
Ethyl 4-(3,4-dimethoxyphenyl)-5,6-dihydro-2-(1,2,4-triazol-1-ylmethyl)-8H-thiopyrano[4',3':4,5]thieno[2,3-b]pyridine-3-carboxylate,
Ethyl 2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-5,6-dihydro-8H-pyrano[4',3':4,5]thieno[2,3-b]pyridine-3-carboxylate,
Ethyl 2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-7-methyl-5,6,7,8-tetrahydrothieno[2,3-b:5,4-c']dipyridine-3-carboxylate,
Ethyl 7-benzyl-2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-5,6,7,8-tetrahydrothieno[2,3-b:5,4-c']dipyridine-3-carboxylate,
Ethyl 7-benzyl-4-(3,4-dimethoxyphenyl)-5,6,7,8-tetrahydro-2-(1,2,4-triazol-1-ylmethyl)thieno[2,3-b:5,4-c']dipyridine-3-carboxylate,
Ethyl 7-benzyl-4-(3,5-dimethoxyphenyl)-5,6,7,8-tetrahydro-2-(1-methylimidazol-2-ylthiomethyl)thieno[2,3-b:5,4-c']dipyridine-3-carboxylate,
Ethyl 2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-7-propyl-5,6,7,8-tetrahydrothieno[2,3-b:5,4-c']dipyridine-3-carboxylate,
Ethyl 7-(4-methoxybenzyl)-4-(3,4-dimethoxyphenyl)-2-pyrrolidinomethyl-5,6,7,8-tetrahydrothieno[2,3-b:5,4-c']dipyridine-3-carboxylate.

(15) A method of producing a compound represented by the formula (I-2)



(I-1)

wherein R^1, R^2, R and ring A are of the same meaning as defined in Claim 1, X' is an oxygen atom or a sulfur atom and Y' is a nitrogen atom or C-G' (G' is an esterified carboxyl group); which is characterized by allowing a compound represented by the formula (II-1)



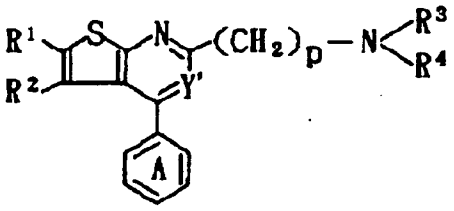
(II-1)

wherein Q is a leaving group; and other symbols are of the same meaning as defined above, to react with a compound represented by the formula (III)

R-X'H (III)

wherein X' and R are of the same meaning as defined above.

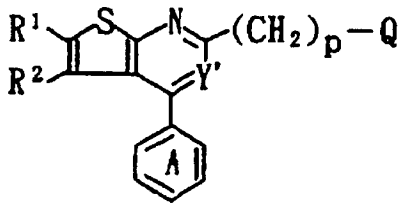
(16) A method of producing a compound represented by the formula (I-2)



(I-2)

wherein R^1, R^2 and ring A are of the same meaning as defined in Claim 1; R^3 and R^4 independently stand for a hydrogen atom, an optionally substituted hydrocarbon residue or an optionally substituted heterocyclic

group, or R^3 and R^4 may be combined to form a nitrogen containing ring; Y' stands for a nitrogen atom or C-G' (G' is an esterified carboxyl group); and p is an integer of 1 to 6, which is characterized by allowing a compound represented by the formula (II-2)



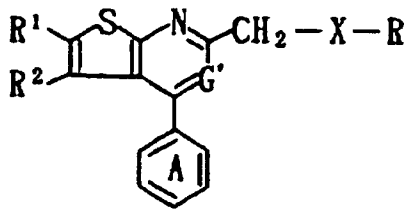
(II-2)

wherein Q is a leaving group; and other symbols are of the same meaning as defined above, to react with a compound represented by the formula (IV)

$$HNR^3R^4 \qquad (IV)$$

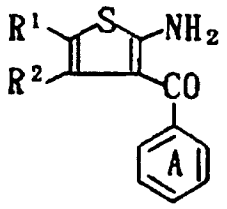
wherein R^3 and R^4 are of the same meaning as defined above.

(17) A method of producing a compound represented by the formula (I-2)



(I-4)

wherein R^1, R^2, X, R and ring A are of the same meaning as defined in Claim 1; and G' is an esterified carboxyl group; which is characterized by allowing a compound represented by the formula (VIII)



(VIII)

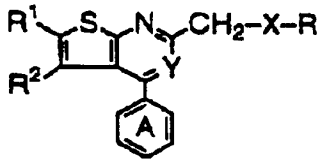
wherein R^1, R^2 and ring A are of the same meaning as defined above, to react with a compound represented by the formula

(IX)

$$R\text{-}X\text{-}CH_2COCH_2\text{-}G' \qquad (IX)$$

wherein R, X and G' are of the same meaning as defined above.

(18) A composition which comprises a compound represented by the formula (I):



(I)

wherein R^1 and R^2 independently stand for a hydrogen atom, a halogen atom or an optionally substituted alkyl group, or R^1 and R^2 may be combined to form an optionally substituted 5- to 7-membered ring; Y is a nitrogen atom or C-G, G is an optionally esterified carboxyl group; X is an oxygen atom, an optionally oxidated sulfur atom or $-(CH_2)_q-$ (q is an integer of 0 to 5); R is an optionally substituted heterocyclic group or an optionally substituted amino group; and ring A may optionally be substituted; or a salt thereof.

(19) The pharmaceutical composition which comprises a compound of the above item (18).

(20) The pharmaceutical composition of the above item (19), which is for the prophylaxis or treatment of

an inflammatony disease.

(21) The pharmaceutical composition of the above item (19), which is for promoting anti-pyretic analgesic action.

(22) The pharmaceutical composition of the above item (19), which is for the prophylaxis or treatment of arthritis.

(23) The pharmaceutical composition of the above item (19), which is for inhibiting bone resorption.

(24) The pharmaceutical composition of the above item (19), which is for the prophylaxis or treatment of osteoporosis.

(25) The pharmaceutical composition of the above item (19), which is for supressing the production of cytokine in a mammal.

(26) A method for the prophylaxis or treatment of an inflammatony disease in a mammal which comprises administering a pharmaceutically effective amount of a compound of the above item (18) to said mammal in need thereof.

(27) A method for the prophylaxis or treatment of osteoporosis in a mammal which comprises administering a pharmaceutically effective amount of a compound of the above item (18) to said mammal in need thereof.

(28) Use of a compound of the above item (1), or a pharmaceutically acceptable salt thereof for the manufacture of a medicament to be used as an anti-inflammatory agent.

(29) Use of a compound of the above item (1), or a pharmaceutically acceptable salt thereof for the manufacture of a medicament to be used for inhibiting bone resorption.

BEST MODE FOR CARRYING OUT THE INVENTION

Various definitions included in the above-general formulae and in the scope of the present invention are

hereinafter described in detail with preferable examples thereof.

In the above-mentioned formula (I), the optionally substituted amino group for R is represented by $-N(R^3)(R^4)$, wherein R^3 and R^4 respectively stand for a hydrogen atom, an optionally substituted hydrocarbon residue or an optionally substituted heterocyclic group, or R^3 and R^4 are combined to form a nitrogen containing cyclic group.

The hydrocarbon residue in the optionally substituted hydrocarbon residue for R^3 or R^4 includes independently, for example, aliphatic hydrocarbon residues, alicyclic hydrocarbon residues, alicyclic-aliphatic hydrocarbon residues, aromatic-aliphatic hydrocarbon residues or aromatic hydrocarbon residues.

Examples of the aliphatic hydrocarbon residues include C_{1-8} saturated aliphatic hydrocarbon residues (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl, isohexyl, heptyl, octyl); and C_{2-8} unsaturated aliphatic hydrocarbon residues (e.g., ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl, 1-octenyl, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl, 1-heptynyl, 1-octynyl).

Examples of the alicyclic hydrocarbon residues include C_{3-7} saturated alicyclic hydrocarbon residues (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl); and C_{5-7} unsaturated alicyclic hydrocarbon residues (e.g., 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-

cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl, 2,4-cycloheptadienyl).

Examples of the alicyclic-aliphatic hydrocarbon residues include, among those formed by bondage of the above-mentioned alicyclic hydrocarbon residue and above-mentioned aliphatic hydrocarbon residue, C_{4-9} ones such as cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3-cyclohexenylmethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl and cycloheptylethyl.

Examples of the aromatic-aliphatic hydrocarbon residues include C_{7-9} phenylalkyl such as benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and 1-phenylpropyl; and C_{11-13} naphtylalkyl such as α-naphthylmethyl, α-naphthylethyl, β-naphthylmethyl and β-naphthylethyl.

Examples of the aromatic hydrocarbon residues include phenyl and naphthyl (e.g., α-naphthyl, β-naphthyl, and so on).

The heterocyclic group in the optionally substituted heterocyclic group for R^3 or R^4 includes independently (i) 5- to 7-membered heterocyclic groups containing one sulfur atom, one nitrogen atom or one oxygen atom; (ii) 5- to 6-membered heterocyclic groups containing 2 to 4 nitrogen atoms; or (iii) 5- to 6-membered heterocyclic groups containing 1 to 2 nitrogen atoms and one sulfur atom or one oxygen atom. (iv) These heterocyclic groups may be condensed with a 6-membered ring containing one or two nitrogen atoms, benzene ring or a 5-membered ring containing one sulfur atom. These are exemplified by aromatic monocyclic-heterocyclic group, aromatic condensed heterocyclic group, non-aromatic heterocyclic group and so on.

Practical examples of the heterocyclic group in

the optionally substituted heterocyclic group for R^3 or R^4 include independently (i) aromatic monocyclic-heterocyclic groups such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazoly, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl and triazinyl;
(ii) aromatic condensed-heterocyclic groups such as benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl;
and (iii) non-aromatic heterocyclic groups such as oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl and piperazinyl.

R^3 and R^4 may, in some instances, be combined with each other to form a ring, especially nitrogen containg 5- to 7-membered ring. Examples of such $-N(R^3)(R^4)$ include 1-pyrrolidinyl, 1-imidazolidinyl, 1-pyrazolidinyl, 1-piperidyl (piperidino), 1-piperazinyl, 4-morpholinyl (morpholino), 4-thiomorpholinyl,

homopiperazin-1-yl, pyrazol-1-yl, imidazol-1-yl, 1,2,4-triazol-1-yl, 1,2,4-triazol-4-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, tetrazol-1-yl, benzimidazol-1-yl, indol-1-yl and 1H-indazol-1-yl.

As the hydrocarbon residue in the optionally substituted hydrocarbon residue for R^3 or R^4, a straight- or branched-chain C_{1-6}, especially C_{1-4}, alkyl is preferable. Among them, more preferable examples include methyl, ethyl, propyl, isopropyl, butyl and so on.

Preferable examples of $-N(R^3)(R^4)$, wherein R^3 and R^4 are combined each other to form a nitrogen containing ring, which includes 1,2,4-triazol-1-yl, imidazol-1-yl, morpholino, piperidino, pyrrolidino and so on.

The hydrocarbon residue and heterocyclic group for R^3 or R^4 may have 1 to 3 substituents on optionally substitutional positions of the chain or the ring thereof.

Examples of such substituents on the hydrocarbon residue and heterocyclic group for R^3 or R^4 include aliphatic hydrocarbon groups, alicyclic hydrocarbon groups, aryl group, aromatic heterocyclic group, non-aromatic heterocyclic group, halogen atoms, nitro group, optionally substituted amino group, acyl group, optionally substituted hydroxyl group, optionally substituted thiol group and optionally esterified carboxyl group.

Examples of aliphatic hydrocarbon groups as the substituent of hydrocarbon groups and heterocyclic groups for R^3 or R^4 include straight- or branched-chain aliphatic hydrocarbon group, for example, alkyl group, preferably C_{1-10} alkyl group, alkenyl group, preferably C_{2-10} alkenyl group, and alkynyl group, preferably C_{2-10} alkynyl group. Preferable examples of the alkyl group include methyl, ethyl, propyl, isopropyl, butyl,

isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, hexyl, pentyl, octyl, nonyl and decyl. Preferable examples of the alkenyl group include vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and 5-hexenyl. Preferable examples of the alkynyl group include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

Examples of the alicyclic hydrocarbon group as the substituent of hydrocarbon residue and heterocyclic group for R^3 or R^4 include saturated or unsaturated C_{3-8} alicyclic hydrocarbon groups such as C_{3-8} cycloalkyl group, C_{3-8} cycloalkenyl group and C_{4-8} cycloalkadienyl group. Preferable examples of the C_{3-8} cycloalkyl group include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl and bicyclo[3.2.1]octyl. Preferable examples of the C_{3-} cycloalkenyl group include 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl and 3-cyclohexen-1-yl. Preferable examples of the C_{4-8} cycloalkadienyl group include 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl and 2,5-cyclohexadien-1-yl.

The aryl group as the substituent on the hydrocarbon residue and heterocyclic group for R^3 or R^4 is a monocyclic or condensed-polycyclic aromatic hydrocarbon group. Preferable examples of it include phenyl, naphthyl, anthryl, phenanthryl and acenaphthylenyl. Among them, phenyl, 1-naphthyl and 2-

naphthyl are more preferable.

Preferable examples of the aromatic heterocyclic group as the substituent of the hydrocarbon residue and heterocyclic group for R^3 or R^4 include aromatic monocyclic-heterocyclic groups such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl; and aromatic condensed-heterocyclic groups such as benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl.

Preferable examples of the non-aromatic heterocyclic group as the substituent of the hydrocarbon residue and heterocyclic group for R^3 or R^4 include oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl and piperazinyl.

Examples of the halogen atom as the substituent of the hydrocarbon residue and heterocyclic group for R^3

or R^4 include fluorine, chlorine, bromine and iodine. Among them, fluorine and chlorine are especially preferable.

Examples of the optionally substituted amino group as the substituent of the hydrocarbon residue and heterocyclic group for R^3 or R^4 include, in addition to amino group, substituted amino groups, for example, amino groups having one or two of C_{1-10} alkyl groups, C_{2-10} alkenyl groups, C_{2-10} alkynyl groups, aromatic groups, heterocyclic groups or C_{1-10} acyl groups, (e.g., methylamino, dimethylamino, ethylamino, diethylamino, dibutylamino, diallylamino, cyclohexylamino, phenylamino, N-methyl-N-phenylamino, acetylamino, propionylamino, benzoylamino, nicotinoylamino).

Examples of the acyl group as the substituent of the hydrocarbon residue and heterocyclic group for R^3 or R^4 include formyl or groups formed by binding of a C_{1-10} alkyl group, C_{2-10} alkenyl group, C_{2-10} alkynyl group or aromatic group with carbonyl group, (e.g., acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, cyclobutancarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl, crotonyl, 2-cyclohexenecarbonyl, benzoyl, nicotinoyl).

Examples of the optionally substituted hydroxyl group as the substituent of the hydrocarbon residue and heterocyclic group for R^3 or R^4 include hydroxyl group and hydroxyl groups having an appropriate substituent, especially a group which is used as a hydroxyl-protecting group, as exemplified by, alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyloxy, aryloxy and so on.

Preferable examples of the alkoxy group include C_{1-10} alkoxy groups (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy,

heptyloxy, nonyloxy, cyclobutoxy, cyclopentyloxy, cyclohexyloxy).

Preferable examples of the alkenyloxy group include C_{2-10} alkenyloxy groups (e.g., allyloxy, crotyloxy, 2-pentenyloxy, 3-hexenyloxy, 2-cyclopentenylmethoxy, 2-cyclohexenylmethoxy).

Preferable examples of the alkynyloxy group include C_{2-10} alkynyloxy groups (e.g., ethynyloxy, 2-propynyloxy, etc.).

Preferable examples of the aralkyloxy group include phenyl-C_{1-4} alkyloxy groups (e.g., benzyloxy, phenethyloxy).

Preferable examples of the acyloxy group include C_{2-4} alkanoyloxy groups (e.g., acetyloxy, propionyloxy, butyryloxy, isobutyryloxy), C_{3-4} alkenoyloxy groups and C_{3-4} alkynoyloxy groups.

Preferable examples of the aryloxy group include phenoxy, 4-chlorophenoxy and so on.

Examples of the optionally substituted thiol group as the substituent of the hydrocarbon residue and heterocyclic group for R^3 or R^4 include thiol group and thiol groups having an appropriate substituent, especially a group which is used as a thiol-protecting group, as exemplified by alkylthio, alkenylthio, alkynylthio, aralkylthio, acylthio, arylthio and so on.

Preferable examples of the alkylthio group include C_{1-10} alkylthio groups (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio, nonylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio).

Preferable examples of the alkenylthio group include C_{2-10} alkenylthio groups (e.g., allylthio, crotylthio, 2-pentenylthio, 3-hexenylthio, 2-cyclopentenylmethylthio, 2-cyclohexenylmethylthio).

Preferable examples of the alkynylthio group include C_{2-10} alkynylthio groups (e.g., ethynylthio, 2-propynylthio, etc.).

Examples of the aralkylthio group include phenyl-C_{1-4} alkylthio groups (e.g., benzylthio, phenethylthio and so on).

Preferable examples of the acylthio group include C_{2-4} alkanoylthio groups (e.g., acetylthio, propionylthio, butyrylthio, isobutyrylthio).

Preferable examples of the arylthio group include phenylthio, 4-chlorophenylthio and so on.

Examples of the optionally esterified carboxyl group as the substituent of the hydrocarbon residue and heterocyclic group for R^3 or R^4 include, in addition to carboxyl group, alkyloxycarbonyl group, alkenyloxycarbonyl group, alkynyloxycarbonyl group, aralkyloxycarbonyl group, acyloxycarbonyl group and aryloxycarbonyl group.

Examples of the alkyl group in the alkyloxycarbonyl group include C_{1-6} alkyl group (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl).

Examples of the alkenyl group in the alkenyloxycarbonyl group include C_{2-6} alkenyl group (e.g., vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 2-methylallyl).

Examples of the alkynyl group in the alkynyloxycarbonyl group include C_{2-6} alkynyl group (e.g., ethynyl, 2-propynyl).

Examples of the aralkyl group in the aralkyloxycarbonyl group means an aryl-alkyl group. As the aryl group, for example, phenyl or naphthyl is preferable, which may optionally have similar substituents as those which the aryl group, exemplified as the hydrocarbon group shown by R^3 or R^4, may optionally have. As the alkyl group, C_{1-6} lower alkyl

groups (e.g., methyl, ethyl, propyl, butyl and so on) are preferable. Preferable examples of the aralkyl group include benzyl, phenethyl, 3-phenylpropyl, (1-naphthyl)methyl and (2-naphthyl)methyl, and, among them, benzyl and phenethyl are preferable.

Examples of the acyl group in the acyloxycarbonyl group include formyl, C_{2-4} alkanoyl, C_{3-4} alkenoyl, C_{3-4} alkynoyl and so on.

Examples of the aryl group in the aryloxycarbonyl group include phenyl, naphytyl and so on.

The substituent on the hydrocarbon residue and heterocyclic group for R^3 or R^4 may optionally have further one or more, preferably 1 to 3, substituents on appropriate positions. As the substituents, mention is made of similar ones shown as the substituents on the hydrocarbon residue and heterocyclic group for R^3 or R^4, as exemplified by a C_{1-10} lower alkyl group, a C_{2-10} lower alkenyl group, a C_{2-10} lower alkynyl group, C_{3-7} cycloalkyl group, C_{3-7} cycloalkenyl group, C_{4-8} cycloalkadienyl group, aryl group, aromatic heterocyclic group, non-aromatic heterocyclic group, aralkyl group (e.g., aryl-C_{1-6} alkyl), amino group, an N-mono-substituted amino group, an N,N-disubstituted amino group, amidino group, acyl group, carbamoyl group, an N-monosubstituted carbamoyl group (e.g., methylcarbamoyl, ethylcarbamoyl, phenylcarbamoyl), an N,N-disubstituted carbamoyl group (e.g., N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, piperidinocarbamoyl, morpholinocarbamoyl, etc.), sulfamoyl group, an N-monosubstituted sulfamoyl group (e.g., methylsulfamoyl, ethylsulfamoyl, phenylsulfamoyl, p-toluenesulfamoyl), an N,N-di-substituted sulfamoyl group (e.g., N,N-dimethylsulfamoyl, N-methyl-N-phenylsulfamoyl, piperidinosulfamoyl, morpholinosulfamoyl, etc.), carboxyl group, a lower C_{1-10} alkoxycarbonyl group

(e.g., methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, sec-butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl), hydroxyl group, a lower C_{1-10} alkoxy group, a lower C_{2-10} alkenyloxy group, C_{3-7} cycloalkyloxy group, aralkyloxy group, aryloxy group, mercapto group, a lower C_{1-10} alkylthio group, aralkylthio group, arylthio group, sulfo group, cyano group, azido group, nitro group, nitroso group, halogen and so on.

In the above-mentioned formula (I), the heterocyclic group in the optionally substituted heterocyclic group for R is, for example, similar ones to those defined above in reference to R^3 or R^4.

The heterocyclic group in the optionally substituted heterocyclic group for R are exemplified by (i) 5- to 7-membered heterocyclic groups containing one sulfur atom, one nitrogen atom or one oxygen atom; (ii) 5- to 6-membered heterocyclic groups containing 2 to 4 nitrogen atoms; (iii) 5- to 6-membered heterocyclic groups containing 1 to 2 nitrogen atoms and one sulfur atom or one oxygen atom; or (iv) groups formed by condensation of such group with a 6-membered group containing two or less nitrogen atom, benzene ring or a 5-membered ring containing one sulfur atom.

These heterocyclic groups may have 1 to 3 substituents at optionally substitutional positions of the ring. As such substituents, mention is made of similar ones shown as the substituents on the hydrocarbon residue or heterocyclic group for R^3 or R^4. These are exemplified by C_{1-10} aliphatic hydrocarbon groups, C_{3-7} alicyclic hydrocarbon groups, aryl group, aromatic heterocyclic groups, non-aromatic heterocyclic groups, halogen atom, nitro group, optionally substituted amino group, acyl group, optionally substituted hydroxyl group, optionally substituted thiol group, optionally esterified carboxyl group and

so on.

These substituents on the heterocyclic group may optionally have further one or more, preferably 1 to 3, substituents on appropriate positions. As these substituents, mention is made of similar ones as shown above, namely, a C_{1-10} lower alkyl group, a C_{2-10} lower alkenyl group, a C_{2-10} lower alkynyl group, C_{3-7} cycloalkyl group, C_{3-7} cycloalkenyl group, C_{4-8} cycloalkadienyl group, aryl group, an aromatic heterocyclic group, a non-aromatic heterocyclic group, aralkyl group (e.g., aryl-C_{1-6} alkyl), amino group, an N-mono-substituted amino group, an N,N-disubstituted amino group, amidino group, acyl group, carbamoyl group, an N-mono-substituted carbamoyl group, an N,N-disubstituted carbamoyl group, sulfamoyl group, an N-monosubstituted sulfamoyl group, an N,N-disubstituted sulfamoyl group, carboxyl group, a lower C_{1-10} alkoxycarbonyl group, hydroxyl group, a lower C_{1-10} alkoxy group, a lower C_{2-10} alkenyloxy group, C_{3-7} cycloalkyloxy group, aralkyloxy group, aryloxy group, mercapto group, a lower C_{1-10} alkylthio group, aralkylthio group, arylthio group, sulfo group, cyano group, azido group, nitro group, nitroso group, halogen and so on.

Preferable examples of the heterocyclic group in the optionally substituted heterocyclic group for R include 1-pyrrolidinyl, 1-imidazolidinyl, 1-pyrazolidinyl, 1-piperidyl (piperidino), 1-piperazinyl, 4-morpholinyl (morpholino), 4-thiomorpholinyl, homopiperazin-1-yl, pyrazol-1-yl, imidazol-1-yl, 1,2,4-triazol-1-yl, 1,2,4-triazol-4-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, tetrazol-1-yl, benzimidazol-1-yl, indol-1-yl and 1H-indazol-1-yl, especially, 1,2,4-triazol-1-yl, imidazol-1-yl, morpholino, piperidino, pyrrolidino and so on.

In the above formula (I), examples of the halogen

atoms for R^1 or R^2 include fluorine, chlorine, bromine and iodine. Among them, fluorine and chlorine are preferable.

In the above formula (I), examples of the alkyl group in the optionally substituted alkyl group for R^1 or R^2 include straight-chain C_{1-6} alkyl or branched-chain C_{3-6} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, sec-pentyl, hexyl, expecially methyl, ethyl propyl and so on.

In the above formula (I), as the substituent of the optionally substituted alkyl groups for R^1 or R^2, mention is made of aliphatic chain hydrocarbon groups, alicyclic hydrocarbon groups, aryl group, aromatic heterocyclic groups, non-aromatic heterocyclic groups, halogen atoms, nitro group, optionally substituted amino group, acyl group, optionally substituted hydroxyl group, optionally substituted thiol group, optionally esterified or amidated carboxyl group and so on. As such aliphatic chain hydrocarbon groups, alicyclic hydrocarbon groups, aryl group, aromatic heterocyclic groups, non-aromatic heterocyclic groups, halogen atoms, nitro group, optionally substituted amino group, acyl group, optionally substituted hydroxyl group, optionally substituted thiol group and optionally esterified carboxyl group, mention is made of such ones as similar to those exemplified as the substituents on the hydrocarbon residue or heterocyclic group shown by the above R^3 and R^4. As the amidated carboxyl group, mention is made of ones represented by $-CON(R^3)(R^4)$, wherein R^3 and R^4 are of the same meaning as defined above.

Or, R^1 and R^2 may be combined with each other to form a 5- to 7-membered ring formed together with the carbon atoms on the thiophene ring. The 5- to 7-membered ring comprising R^1 and R^2 is (i) C_{5-7} alicyclic

hydrocarbon groups, or (ii) heterocyclic group containing one to 4 oxygen atom, one to 4 sulfur atom which may be oxidized, or one nitrogen atom which may be substituted by C_{1-10} alkyl, preferably C_{1-4} alkyl which may be substituted. The 5- to 7- membered ring is represented by the formula of $-R^1-R^2-$, which is for example,
$-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-CH_2-N(R^5)-CH_2-CH_2-$ (R^5 stands for a C_{1-4} alkyl group which may be substituted by phenyl), $-CH_2-S-CH_2-CH_2-$, $-CH_2-SO-CH_2-CH_2-$, $-CH_2-SO_2-CH_2-CH_2-$, or $-CH_2-O-CH_2-CH_2-$, preferably, $-CH_2N(R^5)-CH_2-CH_2-$ (R^5 stands for methyl, ethyl, propyl, benzyl etc.). The C_{1-4} alkyl group for R^5 may have a phenyl group which may be substituted at optionally substitutional positions of the chain.

The phenyl group on the C_{1-4} alkyl group for R^5 may optionally have one or more, preferably 1 to 3, substituents on its substitutional positions. As the substituents, mention is made of similar ones shown as the substituents on the hydrocarbon residue and heterocyclic group for R^3 or R^4, as exemplified by a C_{1-10} lower alkyl group, a C_{2-10} lower alkenyl group, a C_{2-10} lower alkynyl group, C_{3-7} cycloalkyl group, C_{3-7} cycloalkenyl group, C_{4-8} cycloalkadienyl group, aryl group, aromatic heterocyclic group, non-aromatic heterocyclic group, aralkyl group (e.g., aryl-C_{1-6} alkyl), amino group, an N-mono-substituted amino group, an N,N-di-substituted amino group, amidino group, acyl group, carbamoyl group, an N-mono-substituted carbamoyl group (e.g., methylcarbamoyl, ethylcarbamoyl, phenylcarbamoyl), an N,N-di-substituted carbamoyl group (e.g., N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, piperidinocarbamoyl, morpholinocarbamoyl, etc.), sulfamoyl group, an N-mono-substituted sulfamoyl group (e.g., methylsulfamoyl, ethylsulfamoyl,

phenylsulfamoyl, p-toluenesulfamoyl), an N,N-di-substituted sulfamoyl group (e.g., N,N-dimethylsulfamoyl, N-methyl-N-phenylsulfamoyl, piperidinosulfamoyl, morpholinosulfamoyl, etc.), carboxyl group, a lower C_{1-10} alkoxycarbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, sec-butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl), hydroxyl group, a lower C_{1-10} alkoxy group, a lower C_{2-10} alkenyloxy group, C_{3-7} cycloalkyloxy group, aralkyloxy group, aryloxy group, mercapto group, a lower C_{1-10} alkylthio group, aralkylthio group, arylthio group, sulfo group, cyano group, azido group, nitro group, nitroso group, halogen and so on.

R^5 is preferably C_{1-3} alkyl (especially, methyl, ethyl, propyl, isopropyl etc.), or phenyl C_{1-3} alkyl (especially, benzyl, phenetyl, 4-methoxybenzyl, etc.).

Preferable examples of optionally substituted 5- to 7-membered ring ($-R^1-R^2-$) include $-CH_2-N(CH_3)-CH_2-CH_2-$, $-CH_2-N(-CH_2-C_6H_5)-CH_2-CH_2-$, $-CH_2-N(-CH_2-C_6H_4-OCH_3)-CH_2-CH_2-$ and so on.

In the above-mentioned formula (I), Y is a nitrogen atom or C-G, wherein G is an optionally esterified carboxyl group. The optionally esterified carboxyl group is represented by the formula $-COOR^6$ (R^6 is a hydrogen atom, alkyl group, aralkyl group or aryl group).

As the alkyl group for R^6, mention is made of C_{1-6} alkyl groups such as methyl ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl. The aralkyl group for R^6 means the alkyl group having aryl group as the substituent (e.g., aryl-C_{1-6} alkyl group). Examples of the aryl group include phenyl, naphthyl and so on. The aralkyl group for R^6 includes, for example, benzyl, phenethyl, 3-phenylpropyl, (1-naphthyl)methyl and (2-

naphthyl)methyl. As the aryl group for R^6, mention is made of, for example, phenyl and naphthyl.

Preferable examples of Y is C-$COOR^6$ (R^6 is C_{1-4} alkyl), more preferably C-$COOC_2H_5$.

In the above-mentioned formula (I), X is an oxygen atom, an optionally oxidized sulfur atom or $-(CH_2)_q-$, wherein q is an integer of 0 to 5, preferably an integer of 0 to 3.

The optionally oxidized sulfur atom for X is thio group, sulfinyl group or sulfonyl group. Among them, thio group is preferable. The group $-(CH_2)_q-$(wherein q is 0) represented by X is more preferable.

In the formula (I), the ring A may optionally have a substituent, as exemplified by a halogen atom, nitro group, an optionally substituted alkyl group, an optionally substituted hydroxyl group, an optionally substituted thiol group, an optionally substituted amino group, an acyl group, an optionally esterified carboxyl group, an optionally substituted aromatic cyclic group and so on.

Examples of the halogen atom as the substituent on the ring A include fluorine, chlorine, bromine and iodine. Among them, fluorine and chlorine are especially preferable.

Examples of the optionally substituted alkyl group as the substituent on the ring A include C_{1-10} straight-chain alkyl group, C_{3-10} branched-chain alkyl group or C_{3-10} cyclic alkyl group, as exemplified by methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and so on.

Examples of the optionally substituted hydroxyl group as the substituent of the ring A include hydroxyl group and a hydroxyl group having an appropriate substituent, especially a group which is used as a

hydroxyl-protecting group, such as, alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, acyloxy and aryloxy. Preferable examples of the alkoxy include C_{1-10} alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy, nonyloxy, cyclobutoxy, cyclopentyloxy, coclohexyloxy). Preferable examples of the alkenyloxy include C_{2-10} alkenyloxy (e.g., allyloxy, crotyloxy, 2-pentenyloxy, 3-hexenyloxy, 2-cyclopentenylmethoxy, 2-cyclohexenylmethoxy). Preferable examples of the alkynyloxy include C_{2-10} alkynyloxy (e.g., ethynyloxy, 2-propynyloxy, etc.).

Preferable examples of the aralkyloxy include, for example, phenyl-C_{1-4} alkyloxy (e.g., benzyloxy , phenethyloxy, and so on). Preferable examples of the acyloxy include C_{2-4} alkanoyloxy (e.g., acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, and so on). Preferable examples of the aryloxy include phenoxy, 4-chlorophenoxy and so on.

Examples of the optionally substituted thiol group as the substituent on the ring A include a thiol group and a thiol group having an appropriate substituent, especially a thiol-protecting group, such as alkylthio, alkenylthine, alkynylthio, aralkylthio, acylthio and arylthio. Preferable examples of the alkylthio include C_{1-10} alkylthio (e.g., methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio, nonylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio). Preferable examples of the alkenylthio include C_{2-10} alkenylthio (e.g., allylthio, crotylthio, 2-pentenylthio, 3-hexenylthio, 2-cyclopentenylmethylthio, 2-cyclohexenylmethylthio, etc.). Preferable examples of the alkynylthio include

C_{2-10} alkynylthio (e.g., ethynylthio, 2-propynylthio, etc.). Preferable examples of the aralkylthio include phenyl-C_{1-4} alkylthio (e.g., benzylthio, phenethylthio and so on). Preferable examples of the acylthio include C_{2-4} alkanoylthio (e.g., acetylthio, propionylthio, butyrylthio, isobutyrylthio and so on). Preferable examples of the arylthio include phenylthio, 4-chlorophenylthio and so on.

Examples of the optionally substituted amino group as the substituent on the ring A include, in addition to amino group, substituted amino groups, for example, amino groups having one or two C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aromatic groups, heterocyclic groups or C_{1-10} acyl groups (e.g., methylamino, dimethylamino, ethylamino, diethylamino, dibutylamino, diallylamino, cyclohexylamino, phenylamino, N-methyl-N-phenylamino, acetylamino, propionylamino, benzoylamino, nicotinylamino, and so on).

Examples of the acyl as the substituent on the ring A include formyl or the acyl groups formed by bondage of C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl group or an aromatic group with carbonyl group (e.g., acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptenoyl, octanoyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl, crotonyl, 2-hexanecarbonyl, benzoyl, nicotinoyl and so on).

Examples of the optionally esterified carboxyl group as the substituent on the ring A include, in addition to carboxyl group, alkyloxycarbonyl group alkenyloxycarbonyl group, alkynyloxycarbonyl group, aralkyloxycarbonyl group, acyloxycarbonyl group and aryloxycarbonyl group. These groups are represented by the formula $-COOR^6$ (R^6 is a hydrogen atom, C_{1-6} alkyl group, aryl-C_{1-6} alkyl group or aryl group). Preferable examples of the alkyl group in the alkyloxycarbonyl

group include C_{1-6} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl. Preferable examples of the aralkyl group in the aralkyloxycarbonyl group means aryl-alkyl group. As the aryl group, for example, phenyl or naphthyl is preferable, which may optionally have similar substituents as those which the aryl group, as exemplified as the hydrocarbon for R^3 or R^4, may optionally have. As the alkyl group, C_{1-6} lower alkyl groups (e.g., methyl, ethyl, propyl, butyl, etc.) are preferable. Preferable examples of the aralkyl group include benzyl, phenethyl, 3-phenylpropyl, (1-naphthyl)methyl and (2-naphthyl)methyl, and, among them, benzyl and phenethyl are more preferable.

Examples of the optionally substituted aromatic cyclic group as the substituent on the ring A include, in addition to C_{6-14} aromatic hydrocarbon groups (e.g., phenyl, naphthyl, anthryl, etc.), aromatic heterocyclic groups (e.g., pyridyl, furyl, thienyl, imidazolyl, thiazolyl, etc.).

Such substituents on the ring A mentioned above may occupy any substitutional position on the ring. The substituent on the ring A is placed, preferably, at 3- and/or 4-position of the ring A. These substituents may be the same as or different from one another, and the number ranges from 1 to 4, preferably 1 or 2. When the substituents on the ring A are adjacent to each other, the adjacent groups may be combined to form a ring shown by $-(CH_2)_m-$ or $-O-(CH_2)_l-O-$, wherein m denotes an integer of 3 to 5, and l denotes an integer of 1 to 3, and these rings include 5- to 7-membered ring formed together with the carbon atoms on the benzene ring.

Preferably, the ring A is substituted with at least one C_{1-6} alkoxy group, preferably C_{1-3} alkoxy group, more preferably at least one methoxy group; or

the same or different two C_{1-3} alkoxy groups, preferably two methoxy groups. More preferably, the ring A is substituted with two methoxy groups at the 3- and 4-positions of the ring A.

In particular, the compound of the formula (I) is preferably that wherein both R^1 and R^2 are methyl, or R^1 and R^2 are combined with each other to form 6-membered nitrogen containing ring in which $-R^1-R^2-$ is $-CH_2-N(R^5)-CH_2-CH_2-$ (R^5 is C_{1-3} alkyl or benzyl), Y is C-G in which G is ethoxycabonyl, -X-R is N,N-diethylamino, 1,2,4-triazol-1-yl, 1-methyl-imidazol-2-ylthio or pyrrolidino, the ring A is substituted with methoxy groups at the 3- and 4-positions of it.

The salt of the object compound of the present invention is preferably a pharmaceutically acceptable salt, exemplified by salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts of organic acids and salts with basic or acidic amino acid. Preferable examples of salts with an inorganic base include alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as calcium salt and magnesium salt; and aluminum salt and ammonium salt. Preferable examples of salts with an organic base include salts with triemthylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine and N,N'-dibenzylethylenediamine. Preferable examples of salts with an inorganic acid include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and phosphoric acid. Preferable examples of salts with an organic acid include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid and p-toluenesulfonic acid. Preferable examples of

salts with a basic amino acid include salts with arginine, lysine and ornithine, while preferable examples with an acidic amino acid include salts with aspartic acid and glutamic acid.

The object compound (I) of this invention can be administered orally or non-orally, along with a pharmaceutically acceptable carrier, in the form of solid preparations such as tablets, capsules, granules and powders, or liquid preparations such as syrups and injections.

As pharmaceutically acceptable carriers, use is made of various organic or inorganic carriers in common use as pharmaceutical materials, including excipients, lubricants, binders and disintegrants for solid preparations; and solvents, solubilizers, suspending agents, isotonizers, buffers and soothing agents for liquid preparations. Other pharmaceutical additives such as preservatives, antioxidants, coloring agent and sweeteners may be used as necessary.

Preferable excipients are, for example, lactose, sucrose, D-mannitol, starch, crystalline cellulose and light silicon dioxide.

Preferable lubricants are, for example, magnesium stearate, calcium stearate, talc and colloidal silica.

Preferable binders are, for example, binding cellulose, sucrose, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropyl methyl cellulose and polyvinyl-pyrrolidone.

Preferable disintegrators are, for example, starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, cross carmellose sodium and carboxymethyl starch sodium.

Preferable solvents are, for example, water for injection, alcohol, propylene glycol, macrogol, sesame oil and corn oil.

Preferable solubilizers are, for example,

polyethylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate and sodium citrate.

Preferable suspending agent include, for example, surfactants such as stearyl triethanolamine, sodium lauryl sulfate, lauryl aminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride and monostearic glycerol; and hydrophilic polymers such as polyvinyl alcohol, polyvinyl pyrrolidone, carboxymethyl cellulose sodium, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and hydroxypropyl cellulose.

Preferable isotonizers are, for example, sodium chloride, glycerol and D-mannitol.

Preferable buffers are, for example, phosphate, acetate, carbonate and citrate buffer solutions.

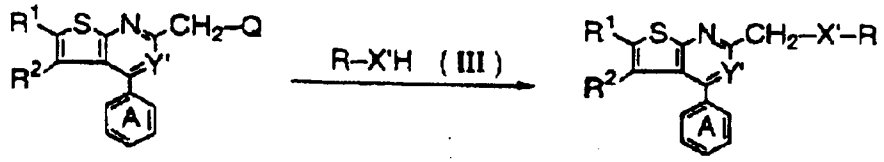
Preferable soothing agents are, for example, benzyl alcohol.

Preferable preservatives are, for example, p-oxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid.

Preferable antioxidants are, for example, sulfites and ascorbic acid.

The above-mentioned compound (I) can be produced by, for example, the following methods, namely:

Method A



(II-1) (I-1)

[wherein Q stands for a leaving group; Y' stands for Nitrogen atom or C-G'; G' stands for an esterified carboxyl group; X' stands for oxygen atom or sulfur atom; and other symbols are of the same meaning as

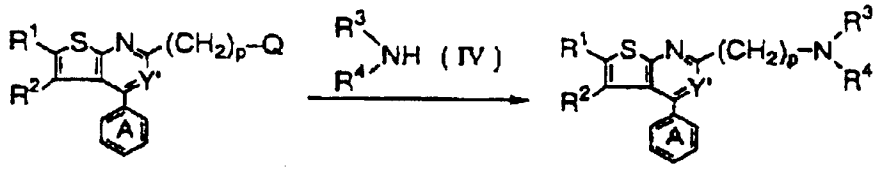
defined above].

In the general formula (II-1), examples of the leaving group shown by Q include halogen, preferably chlorine, bromine or iodine; hydroxyl group activated by esterification, such as a residual group of an organic sulfonic acid (e.g., p-toluenesulfonyloxy group and methanesulfonyloxy group) or a residual group of an organic phosphoric acid, such as diphenylphosphoryloxy group, dibenzylphosphoryloxy group and dimethylphosphoryloxy group; and examples of the esterified carboxyl group shown by G' include groups similar to those exemplified as the esterified carboxyl group shown by G.

In this method, (II-1) is allowed to react with (III) in the presence of a base to produce (I-1). The reaction of (II-1) with (III) is conducted in a proper solvent. Examples of the solvent include aromatic hydrocarbon such as benzene, toluene and xylene; ethers such as dioxane, tetrahydrofuran and dimethoxyethane; alcohols such as methanol, ethanol and propanol; ethyl acetate, acetonitrile, pyridine, N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), chloroform, dichloromethane, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane, acetone, 2-butanone and a mixture of these solvents. The reaction of (II-1) with (III) is conducted in the presence of a proper base, for example, an alkali metal salt such as sodium hydroxide, potassium hydroxide, sodium carbonate and sodium hydrogencarbonate; silver carbonate (Ag_2CO_3), sodium hydride and potassium hydride; and amines such as pyridine, triethylamine, N,N-dimethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane and 1,8-diazabicyclo[5.4.0]undec-7-ene. The amount of these bases to be employed ranges preferably from about 1 to about 5 molar equivalents relative to (II-1). This

reaction conducted at temperature usually ranging from -20°C to 150°C, preferably from about -10°C to 100°C. The thienopyridine or thienopyrimidine derivative (I-1) thus obtained can be isolated and purified by a conventional separating and purifying means such as concentration, concentration under reduced pressure, solvent-extraction, crystallization, recrystallization, phasic transfer and chromatography.

Method B



(II-2) (I-2)

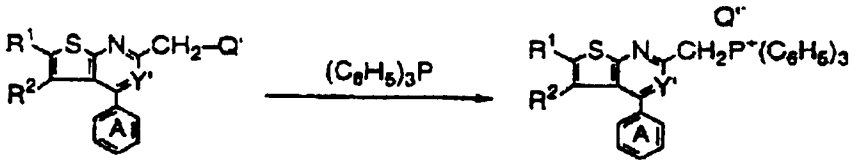
[wherein p denotes an integral number of 1 to 6, and other symbols are of the same meaning as defined above].

In this method, (II-2) is allowed to react with (IV) in the presence of a base to produce (I-2). The reaction of (II-2) with (IV) is conducted in an adequate solvent. Examples of the solvent include aromatic solvent such as benzene, toluene and xylene; ethers such as dioxane, tetrahydrofuran and dimethoxyethane; alcohols such as methanol, ethanol and propanol; ethyl acetate, acetonitrile, pyridine, N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), chloroform, dichloromethane, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane, acetone and 2-butanone; and a mixture of these solvents. The reaction of (II-2) with (IV) is conducted in the presence of an adequate base, as exemplified by an alkali metal salt such as sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate and sodium hydrogencarbonate; amines such as pyridine,

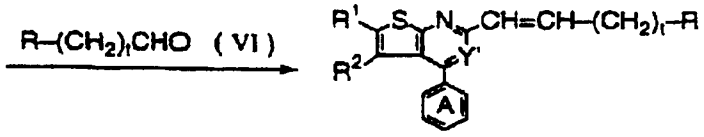
triethylamine and N,N-dimethylaniline; sodium hydride or potassium hydride. The amount of these bases to be employed is preferably in a range from about 1 to about 5 molar equivalents relative to the compound (II-2). This reaction is conducted at temperature usually ranging from -20°C to 150°C, preferably from about -10°C to 100°C. This reaction can be conducted also by using an excess amount of (IV) as the base.

The thienopyridine or thienopyrimidine derivative (I-2) can be isolated and purified by a conventional separating and purifying means, for example, concentration, concentration under reduced pressure, solvent-extraction, crystallization, recrystallization, phasic transfer and chromatography.

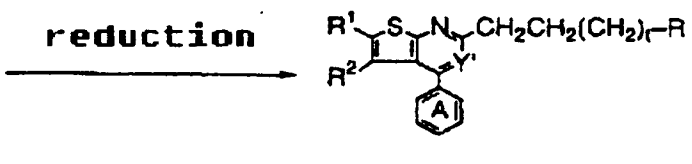
Method C



(II-3) (V)



(VII)



(I-3)

[in formulas (II-3) and (V), Q' stands for a halogen

atom; in formulas (VI), (VII), and (I-3), t denotes an integer of 0 to 4; other symbols are of the same meaning as defined above].

As the halogen atom shown by Q', mention is made of chlorine, bromine and iodine.

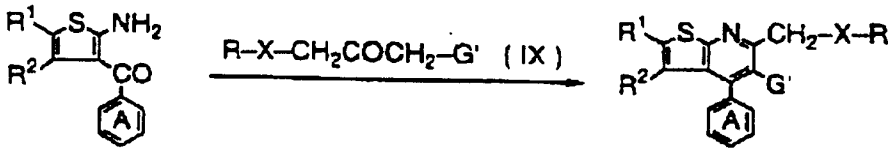
In this method, firstly, the compound represented by the general formula (II-3) is reacted with the equimolar amount of triphenylphosphine to produce the phosphonium salt derivative represented by the general formula (V). This reaction is conducted in a solvent, as exemplified by aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as tetrahydrofuran, dioxane and dimethoxyethane; acetonitrile, and a mixture of these solvent. This reaction is conducted at temperature ranging from 10°C to 200°C, preferably from 30°C to 150°C, for 0.5 to 50 hours.

Then, the phosphonium salt (V) is subjected to condensation reaction with the aldehyde derivative (VI). The condensation of (V) with (VI) is conducted in an adequate solvent in the presence of a base. Examples of the solvent include alcohols such as methanol, ethanol and propanol; ethers such as ethyl ethers, dioxane, tetrahydrofuran and dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; dichloromethane, 1,2-dichloroethane, N,N-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO); and a mixture of these solvents. Examples of the base include alkali metal hydride such as sodium hydride and potassium hydride; alkoxides such as sodium ethoxide, sodium methoxide, potassium ethoxide and potassium tert-butoxide; organic lithium compounds such as methyl lithium and phenyl lithium; and sodium amide. The amount of these bases to be employed ranges preferably from about 1 to about 1.5 molar equivalents relative to the compound (V). This reaction is conducted at

temperature usually ranging from -50°C to 120°C, preferably from -20°C to 80°C. The reaction time ranges from 0.5 to 50 hours. The compound (VII) is obtained as a mixture of (E)-isomer and (Z)-isomer. These isomers, as they are in the form of mixture or after isolating respectively, are subjected to reduction to produce (I-3). This reduction reaction is conducted, in accordance with a conventional method, in a solvent under hydrogen atmosphere in the presence of a catalyst as exemplified by a palladium catalyst (e.g., palladium-carbon and palladium black), a platinum catalyst (e.g., platinum oxide) and Raney nickel. Examples of the solvent include alcohols such as methanol, ethanol and propanol; ethers such as ethyl ether, dioxane, tetrahydrofuran and dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; dichloromethane, 1,2-dichloroethane, ethyl acetate, acetonitrile, acetone, 2-butanone and N,N-dimethylformamide (DMF); and a mixture these solvent. The pressure of hydrogen atmosphere ranges from 1 to 150 atm., preferably from 1 to 20 atm.

The thienopyridine or thienopyrimidine derivative (I-3) thus obtained can be isolated and purified by a conventional means such as concentration, concentration under reduced pressure, solvent-extraction, crystallization, recrystallization, phasic transfer and chromatography.

Method D



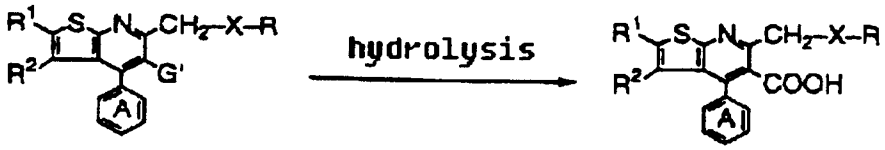
(VIII) (I-4)

[wherein each symbol is of the same meaning as defined above].

In this method, the 2-amino-3-benzoylthiophene derivative (VIII) is allowed to react with (IX) in the presence of an acid to produce (I-4). The reaction of (VIII) with (IX) is conducted in an adequate solvent in the presence of an acid, for example, a Lewis acid such as aluminum chloride and zinc chloride; and hydrochloric acid, sulfuric acid, trifluoroacetic acid and p-toluenesulfonic acid. Examples of the solvent include aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as tetrahydrofuran, dioxane and dimethoxyethane; alcohols such as methanol, ethanol and propanol; N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), chloroform, dichloromethane, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane; and a mixture of these solvents. The amount of the compound (IX) to be employed ranges preferably from 1.0 to 2.0 molar equivalents relative to the compound (VIII). The amount of the acid to be employed ranges, preferably from 0.05 to 2.0 molar equivalents relative to the compound (VIII). This reaction is conducted at temperature usually ranging from 0°C to 200°C, preferably from about 20°C to 120°C. The reaction time ranges from 0.5 to 20 hours, preferably from 1 to 10 hours.

The thienopyridine derivative (I-4) thus obtained can be isolated and purified by a conventional separating and purifying means such as concentration, concentration under reduced pressure, solvent-extraction, crystallization, recrystallization, phasic transfer and chromatography.

Method E



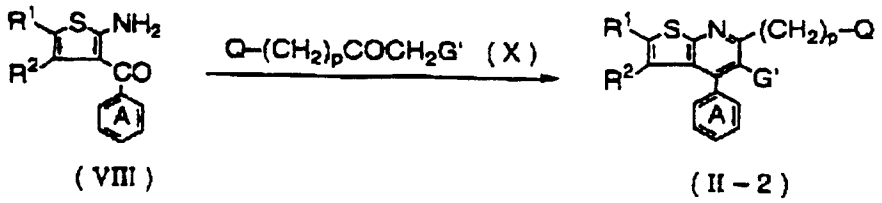
(I-4) (I-5)

In this method, the ester derivative (I-4) is subjected to hydrolysis to produce the carboxylic acid derivative (I-5). The hydrolysis of the compound (I-4) is conducted, in accordance with a conventional method, in water or an aqueous solvent. Examples of the aqueous solvent include alcohols such as methanol, ethanol, 2-methoxyethanol, ethylene glycol, propanol and butanol; ethers such as tetrahydrofuran and dioxane; acetic acid, N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile or acetone. This reaction is conducted in the presence of a base such as potassium carbonate, sodium carbonate, sodium hydroxide and potassium hydroxide, or an acid such as hydrochloric acid, sulfuric acid, acetic acid or hydrobromic acid. Preferably, the acid or the base is employed in an excess amount (base: 1.0 to 10 molar equivalent, acid: 2 to 50 molar equivalents) relative to the compound (I-4). The reaction temperature ranges usually from -20°C to 150°C, preferably from -10°C to 100°C, and the reaction time ranges from 1 to 50 hours.

The thienopyridine derivative (I-5) thus obtained can be isolated and purified by a conventional separating and purifying means such as concentration, concentration under reduced pressure, solvent-extraction, crystallization, recrystallization, phasic transfer and chromatography.

The starting compounds in Method A, Method B and Method C can be produced by, for example, the following method.

Method F



(VIII) (II-2)

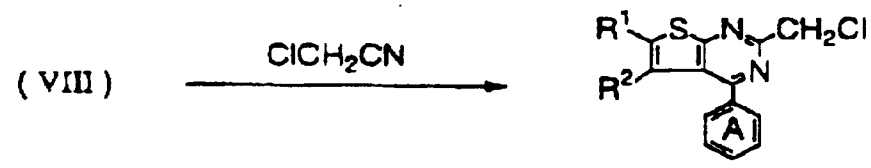
[wherein each symbol is of the same meaning as defined above].

In this method, 2-amino-3-benzoylthiophene derivative (VIII) is allowed to react with (X) in the presence of an acid to produce (II-2). This method is conducted in substantially the same manner as in Method D.

The thienopyridine derivative (II-2) thus obtained can be isolated and purified by a conventional separating and purifying means such as concentration, concentration under reduced pressure, solvent-extraction, crystallization, recrystallization, phasic transfer and chromatography.

The starting compound (VIII) in Method D and Method F can be produced in accordance with the methods described on Journal of Medicinal Chemistry, Vol.16, p.214 (1973), Journal of Medicinal Chemistry, Vol.17, p.624 (1974) and Japanese Patent Unexamined Publication No. 176591/1986. The compound (VIII) can be produced by, for example, substantially the same manner as shown in Reference Examples.

Method G



(VIII) (II-4)

[wherein each symbol is of the same meaning as defined

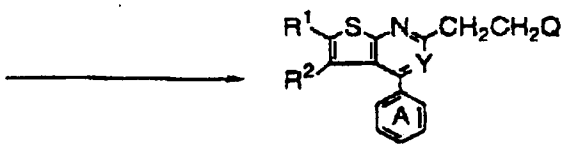
above].

In this method, the 2-amino-3-benzoylthiophene derivative (VIII) is allowed to react with chloroacetonitrile to produce the 2-chloromethyl compound (II-4). The reaction of (VIII) with chloroacetonitrile is conducted in the presence of an acid by using an excess volume of chloroacetonitrile as the solvent. As the acid, use is made of such ones as mentioned in Method D. The amount the acid to be employed ranges from about 1 to about 5 molar equivalents relative to the compound (VIII), preferably 1 to 3 molar equivalents. The reaction time ranges usually from 0.5 to 30 hours, preferably from 1 to 10 hours. The reaction temperature ranges usually from 20°C to 200°C, preferably from 30°C to 150°C.

The thienopyrimidine derivative (II-4) thus obtained can be isolated and purified by a conventional separating and purifying means such as concentration, concentration under reduced pressure, solvent-extraction, crystallization, recrystallization, phasic transfer and chromatography.

Method H

(IX) (X)



(II-5)

[wherein each symbol is of the same meaning as defined

above].

In this method, the compound (IX) is subjected to reduction to produce the alcohol derivative (X), then, from the compound (X), the compound (II-5) is produced.

The reduction of the compound (IX) can be conducted by a per se known method, as exemplified by reduction with a metal hydride, reduction with a metal hydride complex, reduction with diborane or a substituted borane and catalytic hydrogenation. In other words, this reaction is conducted by treating the compound (IX) with a reducing agent. Examples of the reducing agent include alkali metal borohydride (e.g., sodium borohydride and lithium borohydride), a metal hydride complex such as lithium aluminum hydride, metal hydride such as sodium hydride, an organotin compound (e.g., triphenyltin hydride), a metal or metal salt such as a nickel compound and a zinc compound, a catalytic reduction agent using a transition-metal catalyst such as palladium, platinum or rhodium and hydrogen, and diborane. This reaction is conducted in an organic solvent inert to the reaction. Examples of the solvent include aromatic hydrocarbons such as benzene, toluene and xylene; halogenated hydrocarbons such as chloroform, carbon tetrachloride, dichloromethane, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane; ethers such as diethyl ether, tetrahydrofuran and dioxane; alcohols such as methanol, ethanol, propanol, isopropanol and 2-methoxyethanol; amides such as N,N-dimethylformamide; or a mixture of these solvents, and, from among these solvents, a suitable one is selectively employed depending on kinds of the reducing agents. The reaction temperature ranges from -20°C to 150°C, especially preferably from 0°C to 100°C, and the reaction time ranges from about 1 to 24 hours.

Then, the compound (X) is allowed to react with a

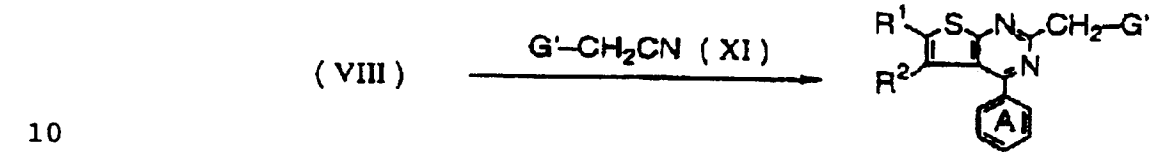
halogenating agent or a sulfonylating agent to produce (II-5). As the halogenating agent, use is preferably made of, for example, thionyl chloride and phosphorus tribromide, and, in this case, (II-5), in which Q is chlorine or bromine, is produced. This reaction is conducted in a suitable inert solvent (e.g., benzene, toluene, xylene, chloroform and dichloromethane) or in an excess volume of a halogenating agent, at temperature ranging from -10°C to 80°C. The amount of the halogenating agent ranges from 1 to 20 mol. relative to (X). As the sulfonylating agent, use is preferably made of, for example, mesyl chloride, tosyl chloride and benzenesulfonyl chloride to yield (II-5) in which Q is mesyloxy, tosyloxy or benzenesulfonyloxy. This reaction is conducted in a suitable inert solvent (e.g., benzene, toluene, xylene, ethyl ether, ethyl acetate, tetrahydrofuran, chloroform and dichloromethane) in the presence of a base (e.g., triethylamine, N-methylmorpholine, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate and potassium carbonate) at temperature ranging from -10°C to 50°C. The amounts of the sulfonylating agent and the base are respectively in the range from 1 to 1.5 molar equivalents relative to one mol. of (X). By allowing 1 to 1.5 mol. of sodium iodide or potassium iodide to react with the compound (II-5) thus produced, in which Q is chlorine, bromine or sulfonyloxy, the compound (II-5) in which Q is iodine can also be produced. In this case, the reaction can be conducted in a solvent such as acetone, methyl ethyl ketone, methanol or ethanol at temperature ranging from 20 to 80°C.

The thienopyridine or thienopyrimidine derivative (II-5) thus obtained can be isolated and purified by a conventional separating and purifying means such as concentration, concentration under reduced pressure,

solvent-extraction, crystallization, recrystallization, phasic transfer and chromatography.

The compound (IX) to be employed in Method H can be produced in accordance with, for example Method I or Method J.

Method I



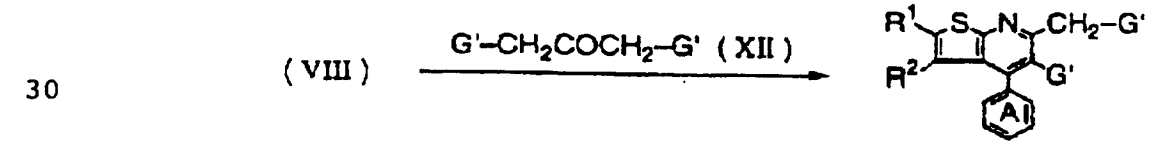
(IX-1)

[wherein each symbol is of the same meaning as defined above].

In this method, the 2-amino-3-benzoylthiophene derivative (VIII) is allowed to react with the cyanoacetic ester derivative (XI) to produce the thienopyrimidine derivative (IX-1). The reaction of (VIII) with (XI) is conducted in substantially the same manner as in Method G.

The thienopyrimidine derivative (IX-1) thus obtained can be isolated and purified by a conventional separating and purifying means such as concentration, concentration under reduced pressure, solvent-extraction, crystallization, recrystallization, phasic transfer and chromatography.

Method J



(IX-2)

[wherein each symbol is of the same meaning as defined above].

In this method, the 2-amino-3-benzoylthiophene

derivative (VIII) is allowed to react with the acetonedicarboxylic acid ester derivative (XII) to produce the thienopyridine derivative (IX-2). The reaction of (VIII) with (XII) is conducted substantially the same manner as in Method D.

The thienopyridine derivative (IX-2) thus obtained can be isolated and purified by a conventional means such as concentration, concentration under reduced pressure, solvent-extraction, crystallization, phasic transfer and chromatography.

Excellent anti-arthritis activities of the compound (I) and its salts provided by the present invention were confirmed in an experimental model of adjuvant arthritis causing arthritis similar to human rheumatoid arthritis. The objective compounds may inhibit the production of cytokines such as interleukin-2 and interferon-γ. And, the toxicity of the compounds of this invention is low. Therefore, the object compounds of this invention can be applied to all types of arthritis presenting inflammatory symptoms at synovial joints of mammalian animals including man (e.g., humans, cattle, horses, swine, dogs, cats, and the like).

And, excellent bone resorption inhibiting activities of the compound (I) and its salts provided by the present invention were confirmed in the experiment as mentioned below. Therefore, the object compounds of this invention can be used as a bone resorption inhibiting agent or an agent for the prophylaxis or treatment of osteoporosis by administering to the above-mentioned mammalian animals including man.

While the dosage of the compound (I) employed in this invention can be selected depending on the administration routes and symptoms of the patients to be treated, it ranges, in oral administration, from 5

mg to 1000 mg per adult person, and, in non-oral administration, from 1 mg to 100 mg once to divided into three times a day.

The test method and its results supporting the pharmacological activities of the compound (I) of this invention or its salts are shown below.

Test Example 1

Action against rat adjuvant arthritis

Male Lewis rats (7 weeks of age, Japan Clea) were sensitized by intracutaneous injection of 0.05 ml of Freund's complete adjuvant (0.5% dead tubercle bacillus cell suspension in liquid paraffin) at the right hind paw. The test drug (25 mg/kg or 12.5 mg/kg), in suspension in 0.5% methyl cellulose, was once daily for 14 days starting just before the sensitization (day 0). On days 0 and 14, the animal's left hind paw volume and body weight were measured by a plethysmometer (Ugo Basile, Italy) and a electric balance (EB-3200D, Shimazu, Japan), respectively, and percent paw swelling suppression and percent body weight gain, relative to non-sensitized control rats, were determined.

The results, expressed in mean ± S.E. for 6 animals in each group, were compared and statistically analyzed by Dunnett's test. Level of significance was set below 5%. As shown in Table 1, the compound of the present invention effectively suppressed paw edema and improved systemic conditions as demonstrated by body weight gain.

Table 1

Compound (Ex.No.)	Dose (mg/kg)	Percent Swelling Suppression (%)	Body Weight Gain[1)] Rate (%)
1	25.0	66**	16**
27	12.5	54**	15*
28	12.5	72**	23**

1) $\frac{\text{(drug-treated rats)-(sensitized control rats)}}{\text{(normal control rats)-(sensitized control rats)}} \times 100\ (\%)$

* ; $p<0.05$
**; $p<0.01$ (relative to control)

Test Example 2

Bone resorption suppressing action

Bone resorption was measured by the method of Raisz [Journal of Clinical Investigation, 44, 103-116(1965)]. Specifically, one Sprague-Dawley rat, at 18 days of gestation, was given 50 μCi of ^{45}Ca (calcium isotope, in $CaCl_2$ solution) by subcutaneous injection. On the following day, the animal was laparotomized and fetal rats aseptically removed. Both forearm bones (radius and ulna) were cut out from the body of each fetus under an anatomical microscope, and connective tissue and cartilages were removed to the maximum possible extent, to prepare bone culture samples. Each bone fragment was pre-cultured at 37°C for 24 hours in 0.6 ml of BGJb medium (Fitton-Jackson modification, GIBCO Laboratories, United States) prepared by adding bovine serum albumin (final concentration 2mg/ml), after which it was transferred to the same medium as above but containing a compound (final concentration 30μM) and cultured for two more days. ^{45}Ca radioactivity in the medium and ^{45}Ca radioactivity in the bone were then measured, and the percent ratio of ^{45}Ca released from the bone to the medium was calculated using the following equation:

$$\text{Percent ratio of } {}^{45}Ca \text{ released from bone to medium} = \frac{[({}^{45}Ca \text{ count in the medium})]}{[({}^{45}Ca \text{ count in the medium}) + ({}^{45}Ca \text{ count in the bone})]} \times 100$$

For control, bone fractions from fetuses of the same litter were cultured for two days in the absence of the test compound. The mean q standard deviation for the values from five bone fragments in a group was calculated, and percent ratio to the control was calculated. The result of compound obtained in Example 27 (bone resorption inhibitory activity) was 76.5%.

Examples

By way of the following Reference Examples and Examples, the present invention will be described in more specifically, but they are not intended to limit the scope of the invention thereto.

Reference Example 1

A solution of ethyl 3,4-dimethoxybenzoate (17.8 g) and acetonitrile (7.0 g) in toluene (30 ml) was added dropwise at 100°C to a suspension of sodium hydride (60% in oil, 6.8 g) in toluene (170 ml) and N,N-dimethylformamide (DMF) (17 ml). The mixture was stirred for three hours at 100°C. The reaction mixture was poured into ice-water. The organic layer was separated. The aqueous layer was acidified with 2N HCl, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$), followed by distilling off the solvent under reduced pressure to leave ω-cyano-3,4-dimethoxyacetophenone (14.0 g, 80%). Recrystallization from ethyl acetate gave colorless needles, m.p.141-142°C.

Reference Example 2

In substantially the same manner as in Reference Example 1, ω-cyano-3,4-methylenedioxyacetophenone was

produced. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p.135-136°C.

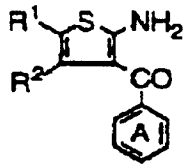
Reference Example 3

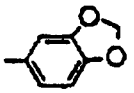
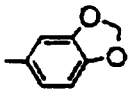
A mixture of ω-cyano-3,4-dimethoxyacetophenone (7.0 g), sulfur (1.2 g), 2-butanone (2.46 g), morpholine (3.5 ml) and ethanol (20 ml) was stirred for two hours under reflux. The reaction mixture was poured into ice-water, which was washed with 2N HCl, 1N KOH and water, successively, then dried ($MgSO_4$), followed by distilling off the solvent under reduced pressure to leave 2-amino-3-(3,4-dimethoxybenzoyl)-4,5-dimethylthiophene (4.1 g, 41%). Recrystallization from ethyl acetate - hexane gave yellow prisms, m.p.172-173°C.

Reference Examples 4 and 5

In substantially the same manner as in Reference Example 3, compounds shown in Table 2 were produced.

Table 2



R.Ex. No.	R^1	R^2	A	m.p. (°C)	Recrystallization solvent
4	CH_3	CH_3		124-125	ethyl acetate-hexane
5	$-(CH_2)_4-$			154-155	ethyl acetate-hexane

Reference Example 6

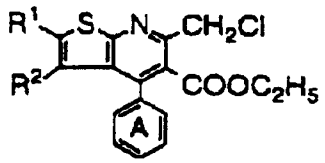
A mixture of 2-amino-3-(3,4-dimethoxybenzoyl)-4,5-dimethylthiophene (3.6 g), ethyl 4-chloroacetoacetate (2.1 g), concentrated sulfuric acid (0. 5 ml) and acetic acid (50 ml) was stirred for two hours at

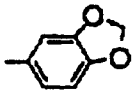
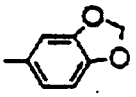
temperature ranging from 90 to 100°C. The reaction mixture was concentrated under reduced pressure. The concentrate was poured into water, which was neutralized with potassium carbonate, followed by extraction with chloroform. The chloroform layer was washed with water and dried ($MgSO_4$), then the solvent was distilled off under reduced pressure. The residue was subjected to column chromatography on silica gel. From the fractions eluted with chloroform-hexane (4:1,v/v), ethyl 6-chloromethyl-4-(3,4-dimethoxyphenyl)-2,3-dimethylthieno[2,3-b]pyridine-5-carboxylate (3.5 g, 67%) was obtained. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p.162-163°C.

Reference Examples 7 and 8

In substantially the same manner as in Reference Example 6, compounds shown in Table 3 were produced.

Table 3



R.Ex. No.	R^1	R^2	A	m.p. (°C)	Recrystallization solvent
7	CH_3	CH_3		148-149	ethyl acetate-hexane
8	$-(CH_2)_4-$			142-143	ethyl acetate-hexane

Reference Example 9

In substantially the same manner as in Reference Example 3, 2-amino-3-(4-chlorobenzoyl)-4,5-dimethylthiophene was produced. Recrystallization from ethyl acetate - hexane gave yellow plates, m.p.122-

123°C.

Reference Example 10

In substantially the same manner as in Reference Example 3, 2-amino-3-(4-chlorobenzoyl)-4-methyl-5-propylthiophene was produced. Recrystallization from ethanol gave yellow prisms, m.p.94-95°C.

Reference Example 11

In substantially the same manner as in Reference Example 3, 2-amino-3-(4-methoxybenzoyl)4,5-dimethylthiophene was produced. Recrystallization from ethyl acetate - hexane gave yellow prisms, m.p.132-133°C.

Reference Example 12

In substantially the same manner as in Reference Example 6, ethyl 6-chloromethyl-4-(4-chlorophenyl)-2,3-dimethylthieno[2,3-b]pyridine-5-carboxylate was produced. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p.132-144°C.

Reference Example 13

In substantially the same manner as in Reference Example 6, ethyl 6-chloromethyl-4-(4-chlorophenyl)-3-methyl-2-propylthieno[2,3-b]pyridine-5-carboxylate was produced. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p.95-96°C.

Reference Example 14

In substantially the same manner as in Reference Example 6, ethyl 6-chloromethyl-4-(4-methoxyphenyl)-2,3-dimethylthieno[2,3-b]pyridine-5-carboxylate. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p.110-111°C.

Reference Example 15

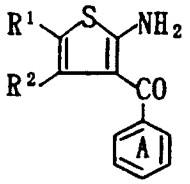
To a mixture of 2-amino-3-(3,4-dimethoxybenzoyl)-4,5-dimethylthiophene (3.0 g) and chloroacetonitrile (11 g) was added, in limited amounts, powdered aluminum chloride (2.75 g). The mixture was stirred for 2.5 hours at 100°C. The reaction mixture was poured into

ice-water, which was subjected to extraction with chloroform. The chloroform layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and water, which was dried ($MgSO_4$). Chloroform was distilled off, and the residue was subjected to column chromatography on silica gel. From the fraction eluted with dichloromethane, 2-chloromethyl-4-(3,4-dimethoxyphenyl)-5,6-dimethylthieno[2,3-d]pyrimidine (1.58 g, 44%) was obtained. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p.117-118°C.

Reference Examples 16 to 31

In substantially the same manner as in Reference Example 3, compounds shown in Table 4 were produced.

Table 4



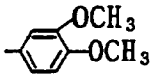
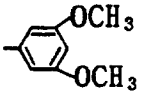
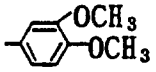
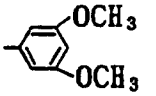
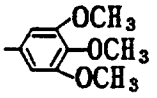
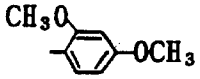
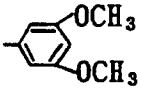
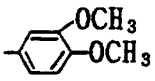
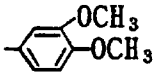
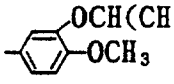
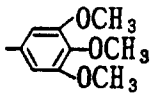
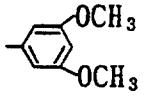
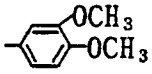
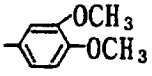
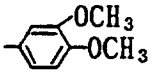
Ref. Ex. No.	R^1	R^2	A	m.p. (℃)	Recrystallization solvent
16	$-CH_2S(CH_2)_2-$			197-198	ethyl acetate-hexane
17	$-CH_2S(CH_2)_2-$			156-157	etanol
18	$-CH_2O(CH_2)_2-$			118-119	ethyl acetate-hexane
19	$-CH_2O(CH_2)_2-$			152-153	ethanol
20	CH_3	CH_3		135-136	ethyl acetate-hexane
21	CH_3	CH_3		181-182	ethyl acetate-hexane
22	CH_3	CH_3		154-155	ethyl acetate-hexane
23	$-CH_2-N(CH_3)-(CH_2)_2-$			180-182	ethanol
24	$-CH_2-N(CH_2C_6H_5)-(CH_2)_2-$			149-150	ethanol
25	CH_3	CH_3		162-163	ethanol

Table 4 (continued)

Ref. Ex. No.	R^1	R^2	A	m.p. (℃)	Recrystallization solvent
26	$-CH_2-N(CH_2C_6H_5)-(CH_2)_2-$			119-120	ethyl acetate-hexane
27	$-CH_2-N(CH_2C_6H_5)-(CH_2)_2-$			157-159	ethyl acetate-hexane
28	$-CH_2-N(C_2H_5)-(CH_2)_2-$			190-192	ethanol
29	$-CH_2-N(C_3H_7)-(CH_2)_2-$			161-162	ethanol
30	$-CH_2-N(CH_2-C_6H_4-OCH_3)-(CH_2)_2-$			165-166	ethanol
31	$-CH_2-N(CH_2C_6H_5)-(CH_2)_2-$			187-188	ethanol

Reference Example 32

A solution of acetonitrile (33.6 g) was added dropwise at -70°C to a mixture of n-butyllithium in hexane (1.6 M, 511 ml) and tetrahydrofuran (900 ml). After the mixture was stirred for 45 minutes at -70°C, a solution of ethyl 2,4-dimethoxybenzoate (86.0 g) in tetrahydrofuran (100 ml) was added dropwise at the same temperature (-70°C). The reaction mixture was stirred for 30 minutes at -70°C, and acidified with 2N HCl. After stirring for 30 minutes at room temperature, the crystals were separated by filtration to leave ω-cyano-2,4-dimethoxyacetophenone (52.3 g, 62%). Recrystallization from ethyl acetate-hexane gave colorless prisms, m.p. 154-155°C.

Reference Example 33

In substantially the same manner as in Reference Example 32, ω-cyano-3,5-dimethoxyacetophenone (52.3 g, 62%) was produced. Recrystalization from ethyl acetate-hexane gave colorless prisms, m.p. 118-119°C.

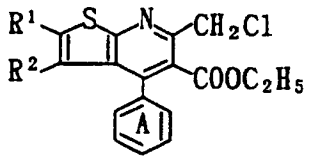
Reference Example 34

In substantially the same manner as in Reference Example 32, ω-cyano-3-isopropoxy-4-methoxyacetophenone (52.3 g, 62%) was produced. Recrystalization from ethyl acetate-hexane gave colorless prism, m.p. 102-104°C.

Reference Examples 35 to 49

In substantially the same manner as in Reference Example 6, compounds shown in Table 5 were produced.

Table 5



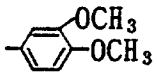
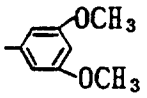
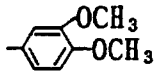
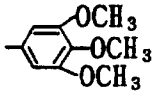
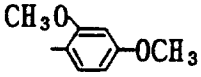
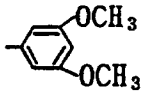
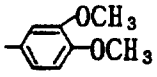
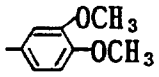
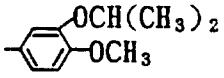
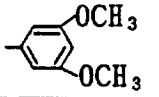
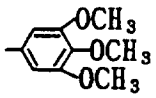
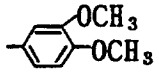
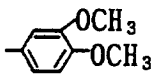
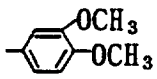
Ref. Ex. No.	R^1	R^2	A	m. p. (℃)	Recrystallization solvent
35	$-CH_2S(CH_2)_2-$			187-188	ethyl acetate-hexane
36	$-CH_2S(CH_2)_2-$			145-146	ethyl acetate-hexane
37	$-CH_2O(CH_2)_2-$			142-143	ethanol
38	CH_3	CH_3		119-120	ethyl acetate-hexane
39	CH_3	CH_3		108-109	ethanol
40	CH_3	CH_3		143-145	ethanol
41	$-CH_2-N(CH_3)-(CH_2)_2-$			98-100	ethanol
42	$-CH_2-N(CH_2C_6H_5)-(CH_2)_2-$			120-121	ethyl acetate-hexane
43	CH_3	CH_3		168-169	ethanol
44	$-CH_2-N(CH_2C_6H_5)-(CH_2)_2-$			135-136	ethyl acetate-hexane

Table 5 (continued)

Ref. Ex. No.	R^1	R^2	A	m.p. (°C)	Recrystallization solvent
45	$-CH_2-N(CH_2C_6H_5)-(CH_2)_2-$			124-125	ethyl acetate-hexane
46	$-CH_2-N(C_2H_5)-(CH_2)_2-$			132-133	ethyl acetate-hexane
47	$-CH_2-N(C_3H_7)-(CH_2)_2-$			136-138	ethyl acetate-ether
48	$-CH_2-N(CH_2-C_6H_4-OCH_3)-(CH_2)_2-$			129-130	ethyl acetate-hexane
49	$-CH_2-N(CH_2C_6H_5)-(CH_2)_2-$			141-142	ethyl acetate-hexane

Example 1

A mixture of ethyl 6-chloromethyl-4-(3,4-dimethoxyphenyl)-2,3-dimethylthieno[2,3-b]pyridine-5-carboxylate (1.5 g), diethylamine (1.04 g) and dichloromethane (35 ml) was stirred for 14 hours under reflux. The reaction mixture was washed with water and dried ($MgSO_4$), then the solvent was distilled off. The residue was subjected to column chromatography on silica gel. From the fraction eluted with chloroform, ethyl 6-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-2,3-dimethylthieno[2,3-b]pyridine-5-carboxylate (1.1 g, 68%) was obtained. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p.110-111°C.

Example 2

Sodium hydride (60% in oil, 0.171 g) was added to a solution of 1H-1,2,4-triazole (0.271 g) in N,N-dimethylformamide (DMF) (15 ml). The mixture was stirred for 15 minutes at room temperature, to which was added ethyl 6-chloromethyl-4-(3,4-dimethoxyphenyl)-2,3-dimethylthieno[2,3-b]pyridine-5-carboxylate (1.5 g). The mixture was stirred for 35 minutes at 80°C. The reaction mixture was poured into water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$), then the solvent was distilled off. The residue was subjected to column chromatography on silica gel. From the fraction eluted with chloroform-methanol (30:1,v/v), ethyl 4-(3,4-dimethoxyphenyl)-2,3-dimethyl-6-(1,2,4-triazol-1-ylmethyl)thieno[2,3-b]pyridine-5-carboxylate (1.0 g, 62%) was obtained. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p.136-137°C.

Example 3

In the column chromatography of Example 2, from the fraction eluted succeeding to ethyl 4-(3,4-

dimethoxyphenyl)-2,3-dimethyl-6-(1,2,4-triazol-1-yl-methyl)thieno[2,3-b]pyridine-5-carboxylate, was obtained ethyl 4-(3,4-dimethoxyphenyl)-2,3-dimethyl-6-(1,2,4-triazol-4-ylmethyl)thieno[2,3-b]pyridine-5-carboxylate (0.12 g, 8%). Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p.187-188°C.

Example 4

In substantially the same manner as in Example 2, ethyl 6-chloromethyl-4-(3,4-methylenedioxyphenyl)-2,3-dimethylthieno[2,3-b]pyridine-5-carboxylate was allowed to react with 1H-1,2,4-triazole to produce ethyl 2,3-dimethyl-4-(3,4-methylenedioxyphenyl)-6-(1,2,4-triazol-1-ylmethyl)thieno[2,3-b]pyridine-5-carboxylate. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p.109-110°C.

Example 5

In the column chromatography of Example 4, from the fraction eluted succeeding to ethyl 2,3-dimethyl-4-(3,4-methylenedioxyphenyl)-6-(1,2,4-triazol-1-ylmethyl)thieno[2,3-b]pyridine-5-carboxylate, was obtained ethyl 2,3-dimethyl-4-(3,4-methylenedioxyphenyl)-6-(1,2,4-triazol-4-ylmethyl)thieno[2,3-b]pyridine-5-carboxylate. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p.96-98°C.

Example 6

A mixture of ethyl 6-chloromethyl-4-(3,4-methylenedioxyphenyl)-2,3-dimethylthieno[2,3-b]pyridine-5-carboxylate (1.5 g), diethylamine (1.36 g) and dichloromethane (35 ml) was stirred for 14 hours under reflux. The reaction mixture was washed with water and dried ($MgSO_4$), then the solvent was distilled off. The residue was subjected to column chromatography on silica gel. From the fraction eluted with chloroform, was obtained ethyl 6-(N,N-diethylaminomethyl)-4-(3,4-methylenedioxyphenyl)-2,3-

dimethylthieno[2,3-b]pyridine-5-carboxylate as an oily product. This oily product was dissolved in ethanol (35 ml), to which was added ethanolic hydrogen chloride (23%, 1.2 g). The mixture was stirred for 15 minutes at room temperature, which was concentrated under reduced pressure to leave hydrochloride of ethyl 6-(N,N-diethylaminomethyl)-4-(3,4-methylenedioxyphenyl)-2,3-dimethylthieno[2,3-b]pyridine-5-carboxylate (0.8 g, 44%) as an amorphous solid product.

NMR(δppm, in $CDCl_3$): 1.03(3H,t,J=7Hz), 1.54(6H,broad s), 1.71(3H,s), 2.48(3H,s), 3.15-3.80(4H, broad), 4.12(2H,q,J=7Hz), 4.50(2H,s), 6.04(1H,d,J=1.4Hz), 6.06(1H,d,J=1.4Hz), 6.65-6.80(1H,d,J=7.6Hz).

Elemental Analysis for $C_{24}H_{29}ClN_2O_4S \cdot 1/2H_2O$:

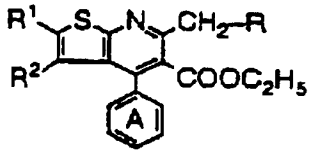
Calcd.: C,59.30; H,6.22; N,5.76

Found: C,59.28; H,6.54; N,5.68

Examples 7 to 9

In substantially the same manner as in Example 2, the compound of Example 7 (Table 6) was obtained. In the column chromatography of Example 7, from the fraction eluted succeedingly, the compound of Example 8 (Table 6) was obtained. In substantially the same manner as in Working Example 6, the compound of Example 9 (Table 6) was produced.

Table 6



Ex. No.	R^1	R^2	A	R	m.p. (°C)	Recrystallization solvent
7	$-(CH_2)_4-$				129-130	ethyl acetate-hexane
8	$-(CH_2)_4-$				-1)	
9	$-(CH_2)_4-$			$-N(C_2H_5)_2$	-2)	

1)NMR(δppm, in $CDCl_3$): 0.95(3H,t,J=7.2Hz), 1.51-2.07(6H,m), 2.80-2.90(2H,m), 4.02(2H,q,J=7.2Hz), 5.39(2H,s), 6.03(1H,d,J=1.2Hz), 6.07(1H,d,J=1.2Hz), 6.68(1H,dd,J=8&2Hz), 6.73(1H,d,J=2Hz), 6.84(1H,d,J=8Hz), 8.34(2H,s).

2)NMR(δppm, in $CDCl_3$): 0.94(3H,t,J=7Hz), 0.99(3H,t,J=7.4Hz), 1.50-2.07(6H,m), 2.52(4H,q,J=7.4Hz), 2.75-2.93(2H,m), 3.84(1H,d,J=13.6Hz), 3.96(2H,q,J=7.4Hz), 3.98(1H,d,J=13.6Hz), 6.00(1H,d,J=1.4Hz), 6.04(1H,d,J=1.4Hz), 6.71(1H,dd,J=8.2&1.6Hz), 6.78(1H,d,J=1.6Hz), 6.82(1H,d,J=8.2Hz).

Example 10

A mixture of ethyl 6-chloromethyl-4-(3,4-dimethoxyphenyl)-2,3-dimethylthieno[2,3-b]pyridine-5-carboxylate (0.75 g), 1-methyl-2-mercaptoimidazole (0.23 g), potassium carbonate (0.28 g) and N,N-dimethylformamide (10 ml) was stirred for one hour at 60°C. The reaction mixture was poured into water, which was subjected to extraction with ethyl acetate.

The ethyl acetate layer was washed with water and dried ($MgSO_4$), then the solvent was distilled off to leave ethyl 4-(3,4-dimethoxyphenyl)-2,3-dimethyl-6-(1-methylimidazol-2-thiomethyl)thieno[2,3-b]pyridine-5-carboxylate (0.39 g, 43%). Recrystallization from ethyl acetate - hexane gave colorless needles, m.p.121-122°C.

Example 11

A mixture of 2-chloromethyl-4-(3,4-dimethoxyphenyl)-5,6-dimethylthieno[2,3-d]pyrimidine (1.0 g), diethylamine (1.2 ml) and dichloromethane (30 ml) was stirred for 16 hours under reflux. The reaction mixture was concentrated under reduced pressure, which was dissolved in ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$), then the solvent was distilled off. The residue was subjected to column chromatography on silica gel. From the fraction eluted with ethyl acetate - methanol (5:1, v/v), was obtained 4-(3,4-dimethoxyphenyl)-5,6-dimethyl-2-(N,N-dimethylamino-methyl)thieno[2,3-d]pyrimidine (0.49 g, 44%). Recrystallization from isopropyl ether gave colorless prisms, m.p.118-120°C.

Example 12

In substantially the same manner as in Example 6, ethyl 4-(4-chlorophenyl)-6-(N,N-diethylaminomethyl)-2,3-dimethylthieno[2,3-b]pyridine-5-carboxylate was produced. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p.98-100°C.

Example 13

In substantially the same manner as in Example 6, ethyl 4-(4-chlorophenyl)-6-(N,N-diethylaminomethyl)-3-methyl-2-propylthieno[2,3-b]pyridine-5-carboxylate was produced. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p.82-83°C.

Example 14

In substantially the same manner as in Example 6, ethyl 6-(N,N-diethylaminomethyl)-4-(4-methoxyphenyl)-2,3-dimethylthieno[2,3-b]pyridine-5-carboxylate was produced. Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p.116-118°C.

Example 15

Sodium hydride (60% in oil, 0.158 g) was added to a solution of 1H-1,2,4-triazole (0.252 g) in N,N-dimethylformamide (DMF) (15 ml). The mixture was stirred for 15 minutes at room temperature, to which was added ethyl 6-chloromethyl-4-(4-chlorophenyl)-2,3-dimethylthieno[2,3-b]pyridine-5-carboxylate (1.2 g). The mixture was stirred for 35 minutes at 80°C. The reaction mixture was poured into water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$), then the solvent was distilled off. The residue was subjected to column chromatography on silica gel. From the fraction eluted with dichloromethane - ethyl acetate (20:1,v/v), was obtained ethyl 4-(4-chlorophenyl)-2,3-dimethyl-6-(1,2,4-triazol-1-ylmethyl)thieno[2,3-b]pyridine-5-carboxylate (0.655 g, 50%). Recrystallization from ethanol gave colorless prisms, m.p.144-145°C.

Example 16

In the column chromatography of Example 15, from the fraction eluted succeeding to ethyl 4-(4-chlorophenyl)-2,3-dimethyl-6-(1,2,4-triazol-1-ylmethyl)thieno[2,3-b]pyridine-5-carboxylate, was obtained ethyl 4-(4-chlorophenyl)-2,3-dimethyl-6-(1,2,4-triazol-4-ylmethyl)thieno[2,3-b]pyridine-5-carboxylate (0.085 g, 7%). Recrystallization from ethyl acetate - hexane gave colorless prisms, m.p.138-139°C.

Examples 17 to 30 and Examples 35 to 41

In substantially the same manner as in Example 1, compounds of Examples 17 to 19, 22 to 28 and 35 to 41

were produced. In substantially the same manner as in Example 2, a compound of Example 20 was produced. The compound of Example 21 was obtained from the fraction eluted succeeding to the compound of Example 20 in the column chromatography of Example 20. In substantially the same manner as in Example 2, a compound of Example 29 was produced. A compound of Example 30 was obtained from the fraction eluted succeeding to the compound of Example 29 in the column chromatography of Example 29.

Example 31

A mixture of the compound (1.2 g) obtained in Reference Example 42, 1H-1,2,4-triazole (0.170 g), potasium carbonate (0.308 g) and acetone (30 ml) was stirred for 9 hours under reflux. The reaction mixture was poured into water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$), then the solvent was distilled off. The residue was subjected to column chromatography on silica gel. From the fraction eluted with ethyl acetate, was obtained a compound of Example 31.

Example 32

A compound of Example 32 was obtained from the fraction eluted succeeding to the compound of Example 31 in the column chromatography of Example 31.

Example 33

A mixture of the compound (1.2 g) obtained in Reference Example 44, imidazole (0.183 g), potassium carbonate (0.308 g) and acetone (30 ml) was stirred for 30 hours under reflux. The reaction mixture was poured into water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$), followed by distilling off the solvent to leave a compond of Example 33.

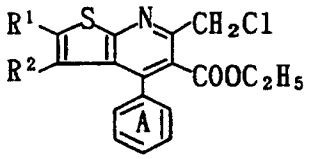
Example 34

A mixture of the compound (1.0 g) obtained in

Reference Example 44, 2-mercapto-1-methylimidazole (0.24 g), potasium carbonate (0.257 g) and N,N-dimethylformamide (10 ml) was stirred for 4 hours at room temperature. The reaction mixture was poured into water, which was subjected to extraction with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$), followed by distilling off the solvent to leave a compound of Example 34.

Compounds of Examples 17 to 41, which were produced as mentioned above, were shown in Table 7.

Table 7



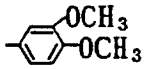
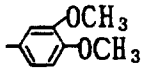
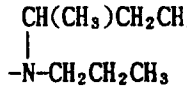
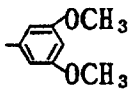
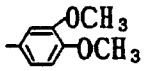
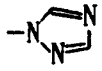
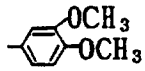
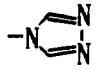
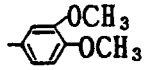
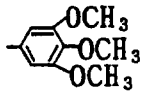
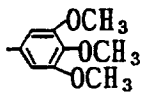
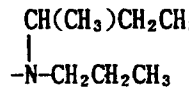
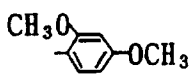
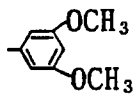
Example No.	R^1	R^2	A	R	m.p. (℃)	Recrystallization solvent
17	$-CH_2S(CH_2)_2-$			$-N(C_2H_5)_2$	115-116	isopropyl ether-hexane
18	$-CH_2S(CH_2)_2-$				93-94	isopropyl ether-hexane
19	$-CH_2S(CH_2)_2-$			$-N(C_2H_5)_2$	128-129	isopropyl ether-hexane
20	$-CH_2S(CH_2)_2-$				160-161	ethyl acetate-hexane
21	$-CH_2S(CH_2)_2-$				206-207	ethyl acetate-hexane
22	$-CH_2O(CH_2)_2-$			$-N(C_2H_5)_2$	149-150	isopropyl ether
23	CH_3	CH_3		$-N(C_2H_5)_2$	117-118	ethyl acetate-hexane
24	CH_3	CH_3			79-80	isopropyl ether-hexane
25	CH_3	CH_3		$-N(C_2H_5)_2$	88-89	ethyl acetate-hexane
26	CH_3	CH_3		$-N(C_2H_5)_2$	87-88	ethyl acetate-hexane

Table 7 (continued)

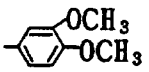
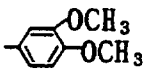
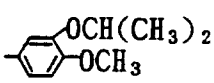
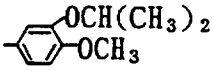
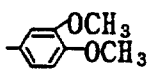
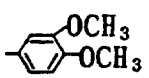
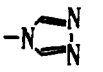
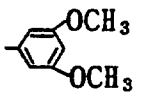
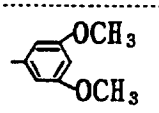
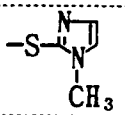
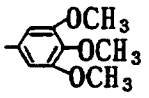
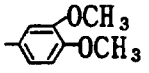
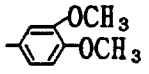
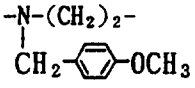
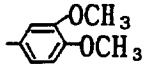
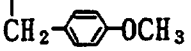
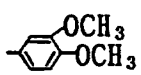
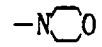
Example No.	R^1	R^2	A	R	m.p. (℃)	Recrystallization solvent
27	$-CH_2-N(CH_3)-(CH_2)_2-$			$-N(C_2H_5)_2$	112-114	ethyl acetate-hexane
28	$-CH_2-N(CH_2C_6H_5)-(CH_2)_2-$			$-N(C_2H_5)_2$	133-134	ethyl acetate-hexane
29	CH_3	CH_3			107-108	ethyl acetate-hexane
30	CH_3	CH_3			187-188	ethyl acetate-hexane
31	$-CH_2-N(CH_2C_6H_5)-(CH_2)_2-$				136-137	ethyl acetate-hexane
32	$-CH_2-N(CH_2C_6H_5)-(CH_2)_2-$				129-130	ethyl acetate-hexane
33	$-CH_2-N(CH_2C_6H_5)-(CH_2)_2-$				168-169	ethanol
34	$-CH_2-N(CH_2C_6H_5)-(CH_2)_2-$				118-119	ethyl acetate-hexane
35	$-CH_2-N(CH_2C_6H_5)-(CH_2)_2-$			$-N(C_2H_5)_2$	105-106	ethyl acetate-hexane
36	$-CH_2-N(C_2H_5)-(CH_2)_2-$			$-N(C_2H_5)_2$	91-93	ethyl acetate-hexane
37	$-CH_2-N(C_3H_7)-(CH_2)_2-$			$-N(C_2H_5)_2$	97-99	ethyl acetate-hexane
38				$-N(C_2H_5)_2$	138-139	ethyl acetate-hexane

Table 7 (continued)

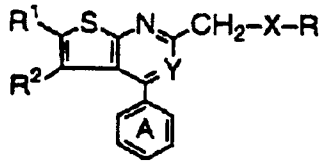
Example No.	R^1	R^2		R	m.p. (℃)	Recrystallization solvent
39	$-CH_2-N-(CH_2)_2-$ 				133-134	ethyl acetate-hexane
40	$-CH_2-N(CH_2C_6H_5)-(CH_2)_2-$				168-169	ethyl acetate-hexane
41	$-CH_2-N(CH_2C_6H_5)-(CH_2)_2-$				183-184	ethyl acetate-hexane

INDUSTRIAL APPLICABILITY

According to the present invention, anti-inflammatory agents, especially novel thienopyridine or thienopyrimidine derivatives useful as a therapeutic agent of arthritis, a useful agent as a bone resorption inhibitor, a method of producing them, a pharmaceutical composition containing same for the prophylaxis or treatment of an inflamatory disease or an osteoporosis are provided.

CLAIMS

1. A compound represented by the formula (I):



(I)

wherein R^1 and R^2 independently stand for a hydrogen atom, a halogen atom or an optionally substituted alkyl group, or R^1 and R^2 may be combined to form a 5- to 7-membered ring; Y stands for a nitrogen atom or C-G, G stands for an optionally esterified carboxyl group; X stands for an oxygen atom, an optionally oxidized sulfur atom or $-(CH_2)_q-$ (q denotes an integer of 0 to 5); R stands for an optionally substituted heterocyclic group or an optionally substituted amino group; and ring A may optionally be substituted, or a salt thereof.

2. The compound of claim 1, wherein the optionally substituted alkyl group for R^1 or R^2 is independently a straight-chain or branched-chain C_{1-6} alkyl group; the optionally substituted 5- to 7-membered ring for R^1 and R^2 is (i) a C_{5-7} alicyclic hydrocarbon group, or (ii) a heterocyclic group containing one to 4 oxygen atom, one to 4 sulfur atom which may be oxidized, or one nitrogen atom which may be substituted by optionally substituted C_{1-10} alkyl; the optionally substituted heterocyclic group for R is (i) a 5- to 7-membered heterocyclic group containing one sulfur atom, one nitrogen atom or one oxygen atom, (ii) a 5- to 6-membered heterocyclic group containing 2 to 4 nitrogen atoms, (iii) a 5- to 6-membered heterocyclic group containing 1 to 2 nitrogen atoms and one sulfur atom or one oxygen atom, or (iv) a group formed by condensation of each of the above three

groups with a 6-membered group containing two or less nitrogen atom, a benzene ring or a 5-membered ring containing one sulfur atom; or the optionally substituted amino group for R is represented by -$N(R^3)(R^4)$, in which R^3 and R^4 independently stand for a hydrogen atom, an optionally substituted hydrocarbon residue or an optionally substituted heterocyclic group, or R^3 and R^4 are combined to form a nitrogen containing cyclic group; and the ring A is substituted by a halogen atom, a nitro group, an optionally substituted alkyl group, an optionally substituted hydroxyl group, an optionally substituted thiol group, an optionally substituted amino group, an acyl group, an optionally esterified carboxyl group or an optionally substituted aromatic cyclic group.

3. The compound of claim 2, wherein the optionally substituted 5- to 7- membered ring for R^1 and R^2 is represented by the formula of $-R^1-R^2-$, which is $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-CH_2-N(R^5)-CH_2-CH_2-$ (R^5 is C_{1-4} alkyl which may be substituted by phenyl), $-CH_2-S-CH_2-CH_2-$, $-CH_2-SO-CH_2-CH_2-$, $-CH_2-SO_2-CH_2-CH_2-$ or $-CH_2-O-CH_2-CH_2-$.

4. The compound of claim 2, wherein the optionally substituted hydrocarbon residue for R^3 or R^4 is independently
a C_{1-8} saturated aliphatic hydrocarbon residue,
a C_{2-8} unsaturated aliphatic hydrocarbon residue,
a C_{3-7} saturated alicyclic hydrocarbon residue,
a C_{5-7} unsaturated alicyclic hydrocarbon residue,
a C_{4-9} alicyclic-aliphatic hydrocarbon residue,
a C_{7-9} phenyl alkyl, a C_{11-13} naphtyl alkyl, a phenyl or a naphthyl;
the optionally substituted heterocyclic group for R^3 or

R^4 is independently (i) a 5- to 7-membered heterocyclic groups containing one sulfur atom, one nitrogen atom or one oxygen atom, (ii) a 5- to 6-membered heterocyclic groups containing 2 to 4 nitrogen atoms, or (iii) a 5- to 6-membered heterocyclic group containing 1 to 2 nitrogen atoms and one sulfur atom or one oxygen atom, which may be condensed with a 6-membered ring containing one or two nitrogen atoms, a benzene ring or a 5-membered ring containing one sulfur atom, and the nitrogen containing cyclic group for R^3 and R^4 is 5- to 7-membered one.

5. The optionally substituted heterocyclic group for R^3 or R^4 is independently an aromatic monocyclic-heterocyclic group, an aromatic condensed heterocyclic group, or a non-aromatic heterocyclic group.

6. The compound of claim 5, wherein (i) the aromatic monocyclic-heterocyclic group for R^3 or R^4 is independently furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl or triazinyl;
(ii) the aromatic condensed heterocyclic group for R^3 or R^4 is independently benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl,

phenanthrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl or 1,2,4-triazolo[4,3-b]pyridazinyl;
or (iii) the non-aromatic heterocyclic group for R^3 or R^4 is independently oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl or piperazinyl.

7. The compound of claim 4, wherein the 5- to 7-membered nitrogen containing cyclic group for R^3 and R^4 is independently
1-pyrrolidinyl, 1-imidazolidinyl, 1-pyrazolidinyl, 1-piperidinyl, 1-piperazinyl, 4-morpholinyl, 4-thiomorpholinyl, homopiperazin-1-yl, pyrazol-1-yl, imidazol-1-yl, 1,2,4-triazol-1-yl, 1,3,4-triazol-1-yl, 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, tetrazol-1-yl, benzimidazol-1-yl, indol-1-yl or indazol-1-yl.

8. The compound of claim 2, wherein the optionally substituted hydrocarbon residue for R^3 or R^4 is independently a straight- or a branched-chain C_{1-6} alkyl.

9. The compound of claim 2, wherein as a substituent for ring A, (i) the halogen atom is fluorine, chlorine, bromine or iodine; (ii) the optionally substituted alkyl group is C_{1-10} straight-chain alkyl, C_{3-10} branched-chain alkyl or C_{3-10} cyclic alkyl; (iii) the optionally substituted hydroxyl group is hydroxyl, C_{1-10} alkoxy, C_{2-10} alkenyloxy, C_{2-10} alkynyloxy, phenyl-C_{1-4} alkyloxy, C_{2-4} alkanoyloxy,

phenoxy or 4-chlorophenoxy; (iv) the optionally substituted thiol group is thiol group, C_{1-10} alkylthio, C_{2-10} alkenylthio, C_{2-10} alkynylthio, phenyl-C_{1-4} alkylthio, C_{2-4} alkanoylthio or phenylthio; (v) the optionally substituted amino group is amino group which may be substituted by C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aromatic group, heterocyclic group or C_{1-10} acyl group; (vi) the acyl group is formyl or ones formed by bondage of C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl or an aromatic group with carbonyl group; (vii) the optionally esterified carboxyl group is a group represented by the formula $-COOR^6$, wherein R^6 is a hydrogen atom, C_{1-6} alkyl group, aryl-C_{1-6} alkyl group or aryl group; (viii) the optionally substituted aromatic cyclic group is C_{6-14} aromatic hydrocarbon group or aromatic heterocyclic group.

10. The compound of claim 1, wherein G is a group represented by the formula $-COOR^6$, whose R^6 is a hydrogen atom, a C_{1-6} alkyl, an aryl-C_{1-6} alkyl or an aryl.

11. The compound of claim 1, wherein X is $-(CH_2)_q-$ (q is an integer of 0 to 3).

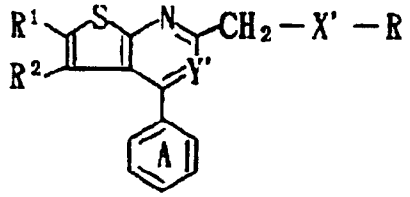
12. The compound of claim 11, wherein q is 0.

13. The compound of claim 1, wherein the ring A is substituted by at least one C_{1-6} alkoxy.

14. The compound of claim 1, which is
Ethyl 6-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-2,3-dimethylthieno[2,3-b]pyridine-5-carboxylate,
4-(3,4-Dimethoxyphenyl)-2-(N,N-diethylaminomethyl)-5,6-

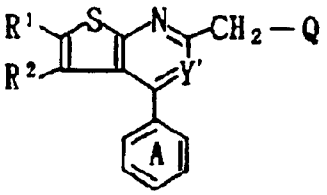
dimethylthieno[2,3-d]pyrimidine,
Ethyl 2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-5,6-dihydro-8H-thiopyrano[4',3'-:4,5]thieno[2,3-b]pyridine-3-carboxylate,
Ethyl 4-(3,4-dimethoxyphenyl)-5,6-dihydro-2-(1,2,4-triazol-1-ylmethyl)-8H-thiopyrano[4',3':4,5]thieno[2,3-b]pyridine-3-carboxylate,
Ethyl 2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-5,6-dihydro-8H-pyrano[4',3':4,5]thieno[2,3-b]pyridine-3-carboxylate,
Ethyl 2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-7-methyl-5,6,7,8-tetrahydrothieno[2,3-b:5,4-c']dipyridine-3-carboxylate,
Ethyl 7-benzyl-2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-5,6,7,8-tetrahydrothieno[2,3-b:5,4-c']dipyridine-3-carboxylate,
Ethyl 7-benzyl-4-(3,4-dimethoxyphenyl)-5,6,7,8-tetrahydro-2-(1,2,4-triazol-1-ylmethyl)thieno[2,3-b:5,4-c']dipyridine-3-carboxylate,
Ethyl 7-benzyl-4-(3,5-dimethoxyphenyl)-5,6,7,8-tetrahydro-2-(1-methylimidazol-2-ylthiomethyl)thieno[2,3-b:5,4-c']dipyridine-3-carboxylate,
Ethyl 2-(N,N-diethylaminomethyl)-4-(3,4-dimethoxyphenyl)-7-propyl-5,6,7,8-tetrahydrothieno[2,3-b:5,4-c']dipyridine-3-carboxylate,
Ethyl 7-(4-methoxybenzyl)-4-(3,4-dimethoxyphenyl)-2-pyrrolidinomethyl-5,6,7,8-tetrahydrothieno[2,3-b:5,4-c']dipyridine-3-carboxylate,

15. A method of producing a compound represented by the formula (I-2)



(I-1)

wherein R^1, R^2, R and ring A are of the same meaning as defined in Claim 1, X' is an oxygen atom or a sulfur atom and Y' is a nitrogen atom or C-G' (G' is an esterified carboxyl group); which is characterized by allowing a compound represented by the formula (II-1)



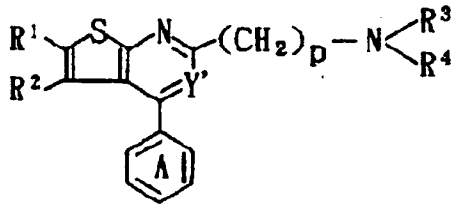
(II-1)

wherein Q is a leaving group; and other symbols are of the same meaning as defined above, to react with a compound represented by the formula
(III)

R-X'H (III)

wherein X' and R are of the same meaning as defined above.

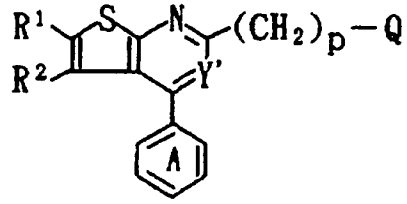
16. A method of producing a compound represented by the formula (I-2)



(I-2)

wherein R^1, R^2 and ring A are of the same meaning as defined in Claim 1; R^3 and R^4 independently stand for a hydrogen atom, an optionally substituted hydrocarbon

residue or an optionally substituted heterocyclic group, or R^3 and R^4 may be combined to form a nitrogen containing ring; Y' stands for a nitrogen atom or C-G' (G' is an esterified carboxyl group); and p is an integer of 1 to 6, which is characterized by allowing a compound represented by the formula (II-2)



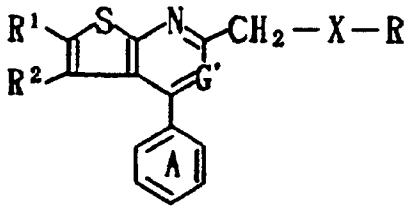
(II-2)

wherein Q is a leaving group; and other symbols are of the same meaning as defined above, to react with a compound represented by the formula (IV)

$$HNR^3R^4 \qquad (IV)$$

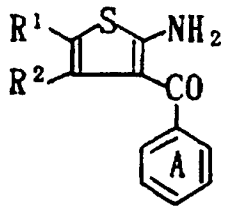
wherein R^3 and R^4 are of the same meaning as defined above.

17. A method of producing a compound represented by the formula (I-2)



(I-4)

wherein R^1, R^2, X, R and ring A are of the same meaning as defined in Claim 1; and G' is an esterified carboxyl group; which is characterized by allowing a compound represented by the formula (VIII)



(VIII)

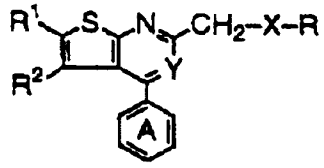
wherein R^1, R^2 and ring A are of the same meaning as defined above, to react with a compound represented by the formula

(IX)

$$R\text{-}X\text{-}CH_2COCH_2\text{-}G' \qquad (IX)$$

wherein R, X and G' are of the same meaning as defined above.

18. A composition which comprises a compound represented by the formula (I):



(I)

wherein R^1 and R^2 independently stand for a hydrogen atom, a halogen atom or an optionally substituted alkyl group, or R^1 and R^2 may be combined to form an optionally substituted 5- to 7-membered ring; Y is a nitrogen atom or C-G, G is an optionally esterified carboxyl group; X is an oxygen atom, an optionally oxidated sulfur atom or $-(CH_2)_q-$ (q is an integer of 0 to 5); R is an optionally substituted heterocyclic group or an optionally substituted amino group; and ring A may optionally be substituted; or a salt thereof.

19. The pharmaceutical composition which comprises a compound of claim 18.

20. The pharmaceutical composition of claim 19, which is for the prophylaxis or treatment of an inflammatony disease.

21. The pharmaceutical composition of claim 19, which is for promoting anti-pyretic analgesic action.

22. The pharmaceutical composition of claim 19, which is for the prophylaxis or treatment of arthritis.

23. The pharmaceutical composition of claim 19, which is for inhibiting bone resorption.

24. The pharmaceutical composition of claim 19, which is for the prophylaxis or treatment of osteoporosis.

25. The pharmaceutical composition of claim 19, which is for supressing the production of cytokine in a mammal.

26. A method for the prophylaxis or treatment of an inflammatony disease in a mammal which comprises administering a pharmaceutically effective amount of a compound of claim 18 to said mammal in need thereof.

27. A method for the prophylaxis or treatment of osteoporosis in a mammal which comprises administering a pharmaceutically effective amount of a compound of claim 18 to said mammal in need thereof.

28. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament to be used as an anti-inflammatory agent.

29. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament to be used for inhibiting bone resorption.

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/JP 95/02271

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D495/04 A61K31/44 A61K31/505 C07D495/14
//(C07D495/04,333:00,221:00),(C07D495/04,333:00,239:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 85, no. 13, 27 September 1976 Columbus, Ohio, US; abstract no. 94398r, M. SHIROKI '2-(2-Carboxyethyl)-4-arylthieno(2,3-d)pyrimidines' page 641; cited in the application see abstract & JP,A,51 043 796 (YOSHITOMI) 14 April 1976 -----	1,18,20

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 February 1996	23.02.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Voyiazoglou, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Ir. .national application No.
PCT/JP 95/02271

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark : Although claims 26-27 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/ composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.